

Ocular Angiogenesis: The Science Behind the Symptoms

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With a variety of factors contributing to neovascularization, many therapies are being developed.

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With most things in nature, a balance must be struck between two opposing forces, each necessary for a functional end product. Enormously complex interactions between production, degradation and reformation are necessary for any living organism. The eye, being one of the most complex and evolved organs, must also adhere to this delicate balance. Angiogenesis and antiangiogenesis are one of these many pairings that must achieve balance. In his groundbreaking 1971 article, Judah Folkman introduced the idea of a “diffusible message” released from solid tumor cells to invoke a robust capillary-sprouting response, more robust than ordinary wound healing or inflammation, to help support its cancerous growth. In the same light, Folkman introduced the concept of antiangiogenesis.¹

A distinction between vasculogenesis and angiogenesis bears mention. Vasculogenesis is blood-vessel formation via endothelial progenitor cells and hemangioblast differentiation, while angiogenesis is the formation of new capillaries from pre-existing blood vessels. Angiogenesis requires endothelial cell migration, proliferation, survival, vessel maturation, vessel-wall remodeling and degradation of the extracellular matrix. It is a normal part not only of development but also of healing. Endothelial cell number is normally stable without significant proliferation, likely due to a balance between proangiogenic factors (ie, vascular endothelial growth factor) and antiangiogenic (angiostasis) factors (ie, pigment epithelium-derived factor). When there is an imbalance between these two, pathology ensues.

Ocular angiogenesis is a major cause of much ocular disease and blindness. It is a significant contributing factor in diabetic retinopathy, exudative AMD, corneal graft rejection, corneal neovascularization, retinopathy of prematurity, retinal vein occlusion, neovascular glaucoma and sickle cell retinopathy. In this article, different forms of ocular angiogenesis, their mediators and implications for treatment will be reviewed.

RETINAL AND CHOROIDAL NEOVASCULARIZATION

Retinal Neovascularization

Proliferative diabetic retinopathy (**Figures 1-3**), RVO and sickle cell proliferative vitreoretinopathy are the most common forms of retinal neovascularization. Other causes include familial exudative vitreoretinopathy, sarcoidosis, pars planitis, radiation retinopathy, ocular ischemic syndrome and Eales disease. A combination of angiogenesis and vasculogenesis occurs during retinal neovascularization. Normally, minimal endothelial cell proliferation occurs in the retina.² “Hypoxia is believed to be the initial stimulus that causes an upregulation of growth factors, integrins and proteinases, which result in endothelial cell proliferation and migration.”³ Hypoxia upregulates VEGF mRNA in retinal endothelial cells, RPE cells, pericytes, Müller cells and ganglion cells.⁴

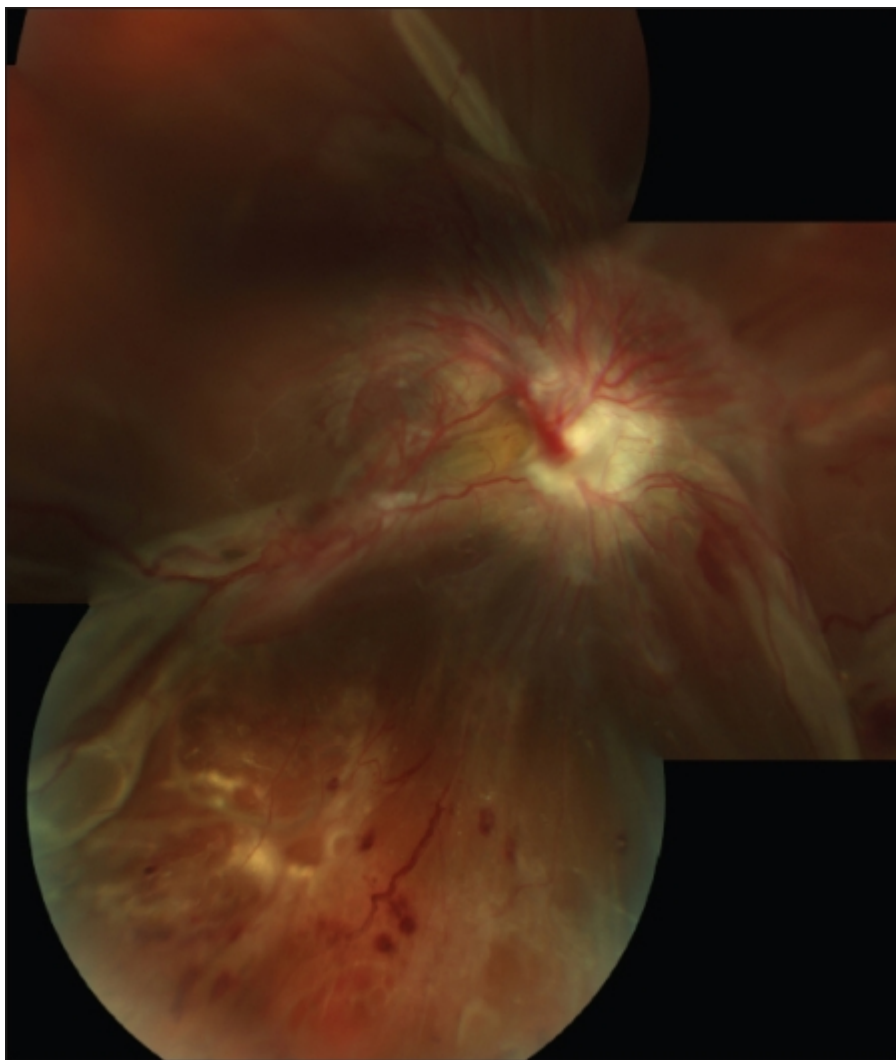
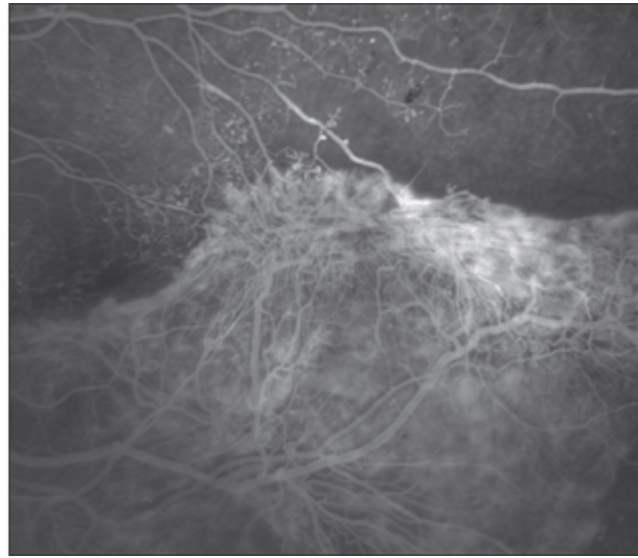
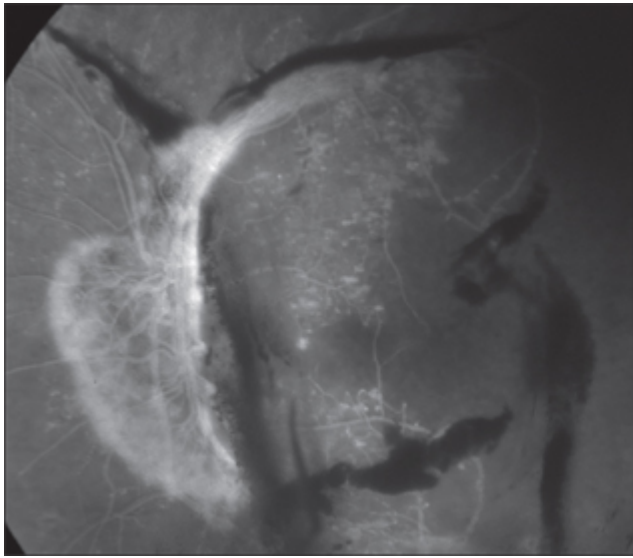


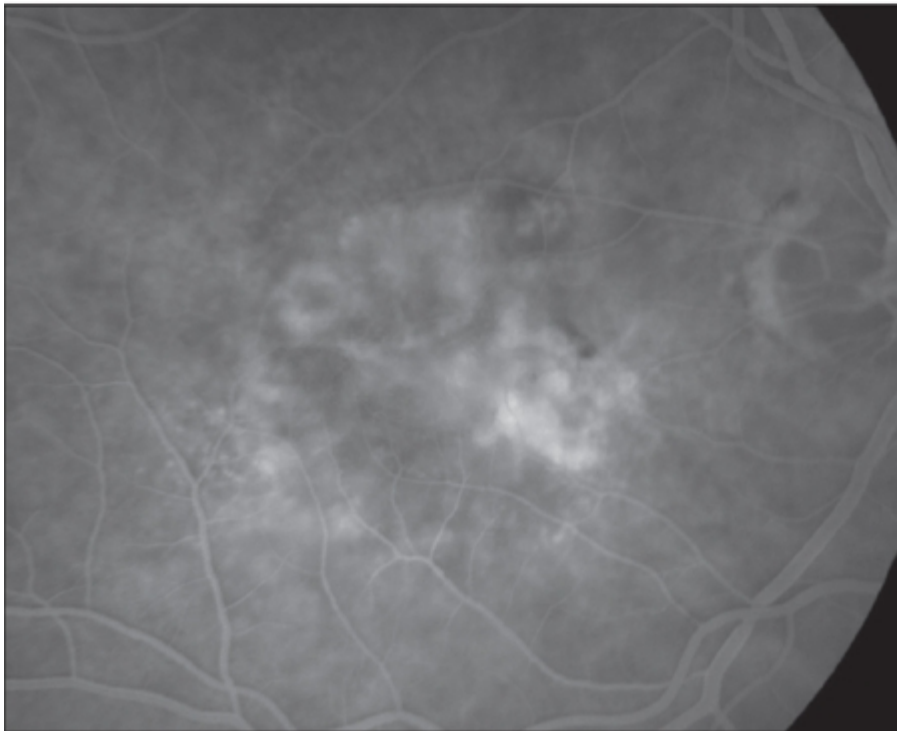
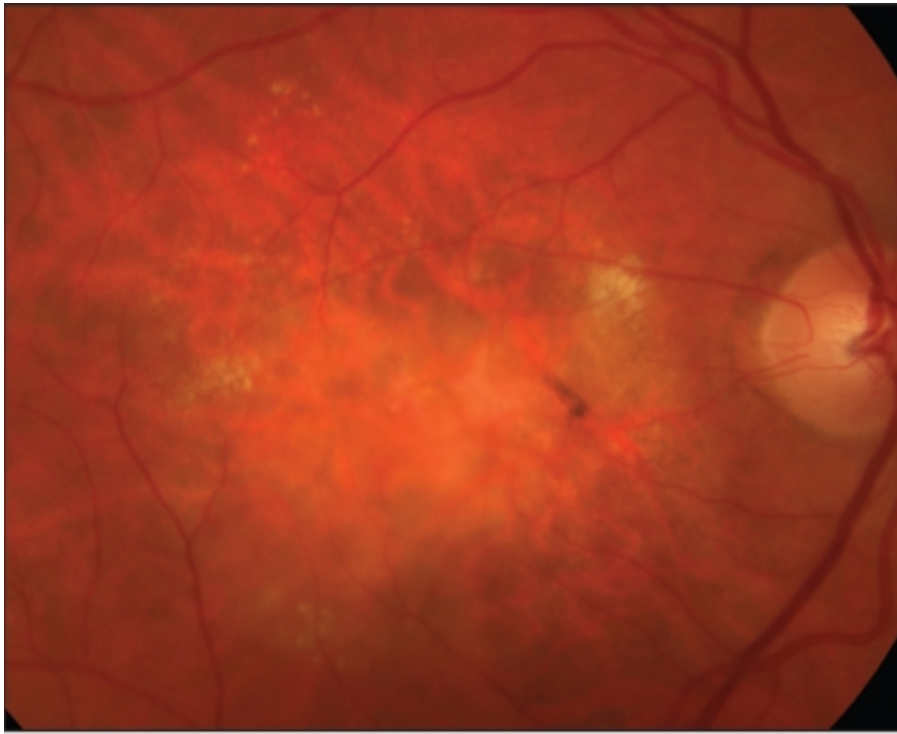
Figure 1. Severe proliferative diabetic retinopathy with tractional retinal detachment.



Figures 2 and 3. Early phase fluorescein angiography of leaking neovascular membranes and hemorrhage in patients with PDR.

Choroidal Neovascularization

Despite alterations in choroidal blood flow in AMD, it may not be enough to produce significant hypoxia to induce CNV.^{3,5,6} Like retinal neovascularization, CNV is a combination of angiogenesis and vasculogenesis.⁷ CNV is most commonly seen in wet AMD (**Figures 4 and 5**). Other common causes are high myopia, choroidal rupture, angioid streaks, ocular histoplasmosis syndrome, multifocal choroiditis, punctate inner choroidopathy and iatrogenic causes (intense laser photocoagulation). Wet AMD is the leading cause of severe vision loss in the elderly in the United States.⁸ Oxidative damage and inflammation (and less so hypoxia) are thought to tip the pro- and antiangiogenic-factor balance in favor of angiogenesis.



Figures 4 and 5. Fundus photography and mid-phase fluorescein angiography of an active choroidal neovascular membrane in a patient with exudative age-related macular degeneration.

INFLAMMATION AND COMPLEMENT

In experimental models, a robust immune response is seen quickly after choroidal neovascular membrane (CNVM) is induced by laser. Within 72 hours, there is an influx of neutrophils, macrophages, natural killer cells, microglial cells and edema.⁹ Macrophages are found near ruptured or thin areas in Bruch's membrane and have been isolated from CNVM removed via submacular surgery.¹⁰ Activated macrophages secrete collagenase and elastase, which may erode Bruch's membrane, allowing for vascular mobilization. Recently, inhibition of vascular adhesion protein-1 decreased macrophage accumulation in CNV lesions and reduced CNV size¹¹ and expression of other inflammatory molecules including TNF- α , ICAM-1 and MCP-1.¹¹

Drusen are likely the byproducts of RPE cells with some protein components, possibly arising from the choroid. It is still not truly known if drusen are epiphenomena of AMD, an active player in the inflammatory cascade, or a passive player via its physical barrier and disruption of transport across Bruch's membrane.¹² Shen was able to produce a CNV membrane by subretinal injection of Matrigel (BD Biosciences, Sparks, MD), a soluble basement membrane preparation mimicking drusen formation.¹³ In the past decade, noting similarities between drusen found in AMD and drusen found in patients with membranoproliferative glomerulonephritis type 2, Hageman and colleagues formed the basis of complement system dysfunction and its role in CNVM formation.¹⁴⁻¹⁶ Specifically, variants of complement factor H (CFH) and alterations in the alternative complement pathway have been genetically linked to AMD.¹⁴⁻¹⁷ A myriad of targets of the complement system exist and several phase 1 and 2 trials are ongoing. Potential agents work by either replacing a defective component (ie, CFH with the Y402H mutation) or by blocking a complement pathway (C3 and C5 inhibitors).¹⁸

VEGF

Vascular endothelial growth factor was initially named vascular permeability factor, as it originally was isolated in tumor ascites fluid from guinea pigs.¹⁹ VEGF is 50,000 times more potent as a vasodilator than histamine.²⁰ It includes a family of growth factors — VEGF-A, VEGF-B, VEGF-C, VEGF-D and PlGF (placental growth factor). The major mediator of tumor angiogenesis is VEGF-A. Despite a very high affinity between VEGF and VEGF receptor 1 (VEGFR-1), most transduction occurs with VEGFR-2. VEGFR-1 may be a “decoy” receptor, preventing VEGF binding to VEGFR-2.^{3,21} Thus, the interaction of VEGF and VEGFR-2 is crucial.

Vascular endothelial growth factor is expressed in most types of human cancers and is highly selective for endothelial cells.^{10,22} As adapted from Hicklin, VEGF is involved in: (1) endothelial cell proliferation via activation of mitogen-activated protein kinases; (2) endothelial cell permeability via opening of endothelial fenestrations and cell junctions; (3) tumor-cell invasion via induction of metallo-proteinases (MMPs) and urokinase plasminogen activators (UPA), hence promoting extracellular matrix degradation; (4) migration through activation of FAK, p38 and nitric oxide; (5) survival of new endothelial cells by inhibiting apoptosis; and (6) activation and stabilization of the vascular network.²³

Induction of VEGF results from hypoxia via hypoxia-inducible factor 1 (HIF-1), low pH, inflammatory cytokines (IL-6), growth factors (basic fibroblast growth factor), sex hormones (androgens and estrogens), chemokines, oncogene activation and decreased activity of tumor suppressor gene activity.^{22,23} Numerous studies have shown increased aqueous and vitreous levels of VEGF and VEGFR-1 in a variety of ocular proliferative conditions.^{24 31} Surgically removed CNVMs from AMD patients show increased VEGF expression in fibroblasts and RPE cells.^{32 34}

But is VEGF itself sufficient enough to produce retinal and choroidal neovascularization? VEGF is found in the Bruch's membrane–choriocapillaris complex of normal healthy donor eyes.^{10,35} Some animal models had difficulty producing both retinal and choroidal neovascularization. Ozaki implanted intravitreal, sustained-release VEGF pellets that induced retinal neovascularization in rabbits but not in primates.³⁶ Tolentino showed that intravitreal injections of VEGF in monkey eyes produced capillary nonperfusion and vessel dilation, but preretinal neovascularization in only the peripheral retina and not posterior pole.³⁷ Transgenic mice in which rhodopsin promoter was coupled to a VEGF gene, hence producing increased intraretinal VEGF, did form intraretinal and subretinal neovascularization. However, as Campochiaro has demonstrated, when increased VEGF levels are combined with photoreceptor degeneration, CNVM may form. Thus, healthy photoreceptors may somehow prevent the choriocapillaris from responding to elevated VEGF levels.^{38,39}

Basic FGF

Fibroblast growth factor (FGF) is a heparin-binding growth factor with a high affinity for heparin sulfate proteoglycans. FGF and associated receptor tyrosine kinases (RTKs) are expressed in virtually all cells — overexpression plays a role in many cancers.⁴⁰ A recent question is whether it is truly involved in retinal and choroidal neovascularization. Studies have shown increased levels of FGF and FGF-like peptides in ischemic retinopathy and laser-induced CNV. Following FGF-impregnated microsphere injection into the subretinal space, AMD-like neovascular membranes formed in rabbit eyes.^{3,41-43} However, other studies suggest that FGF is only angiogenic when it accompanies other cell injury, thus unmasking “control mechanisms that sequester FGF2.”^{3,44} Newer evidence may show that FGF may not, at least alone, be a factor in ocular angiogenesis. FGF2-deficient transgenic mice developed the same amount of retinal and choroidal neovascularization as in wild-type mice. FGF2 retinal overexpression did not produce retinal neovascularization in mice.^{45,46}

IGF-1

The role of insulin-like growth factor (IGF)-1 in angiogenesis was seen as early as 1953, when Poulsen noted regression of neovascularization in proliferative diabetic retinopathy patients after pituitary infarction.⁴⁷ Pituitary ablation was even a treatment for PDR at one time. IGF-1 is elevated in the serum and vitreous in PDR.^{48,49} Elevated growth hormone/IGF-1 has been implicated in retinal neovascularization in mouse models independent of VEGF levels.⁵⁰ More recently, Hellstrom studied the relationship between IGF-1 and VEGF in retinopathy of prematurity. Knock-out IGF-1 mice's normal retinal vascular development was arrested despite adequate VEGF levels. Infants with higher levels of IGF-1 had more normal vasculature development. Hellstrom proposed that infants with a low level of IGF-1 develop an avascular retina, and in conjunction with subsequent elevated VEGF levels, proliferative ROP ensues.⁵¹

MMP/UPA

Extracellular proteinases are vital for the migration of endothelial cells through the extracellular matrix. Urokinase plasminogen activator and the matrix metalloproteinase (MMP) family are primarily involved in angiogenesis. MMPs are upregulated in angiogenic lesions and “their inhibition or genetic ablation diminishes angiogenic switching, tumor size and growth.”^{3,11,52-54}

Prinomostat (AG3340), an MMP inhibitor, was shown to inhibit CNVM growth and leakage when injected intravitreally in an animal model, but early human trials studying use for cancers were terminated. It is currently being studied for possible ocular use.^{55,56} Intravitreal injection of A6, a urokinase system inhibitor, showed promise in successful treatment of monkey CNVM — up to a 76% reduction in CNVM size was safely observed.⁵⁷

IL-8 AND TNF- α

Interleukin-8 is also thought to play a role in the inflammatory component of ocular neovascularization. It is a cytokine that is a chemotactic factor for neutrophils and lymphocytes. IL-8 levels are significantly elevated in the vitreous of patients with proliferative neovascularization, including PDR, RVO and Eales disease.^{31,58} It is also thought to aid in the inflammatory component of angiogenesis as shown in rat cornea studies.⁵⁹ Elner showed that stimulated RPE cells synthesized IL-8, thereby possibly augmenting the inflammatory cascade in angiogenesis.⁶⁰

Elevated levels of TNF- α have been isolated from fibrovascular membranes in PDR eyes,⁶¹ CNV membranes⁶² and animal models of hypoxia-induced retinal neovascularization.⁶³ TNF- α antagonists have been successful in treating T-cell-mediated noninfectious uveitis and juvenile idiopathic arthritis, but its role in ocular angiogenesis has not been well established.

PEDF

Pigment epithelium–derived factor (PEDF) is believed to be the most potent angiogenesis inhibitor. Hypoxia has been shown to downregulate PEDF, thus permitting neovascularization.^{64,65} Vitreous samples from PDR and RVO patients showed lower PEDF levels than in controls, and PDR eyes treated with PRP showed the ability to replenish their levels of PEDF.^{31,66} Systemic and intravitreal PEDF administration decreases retinal neovascularization in a hypoxia-induced neovascularization mouse model.^{67,68} Mori showed decreased CNV using an adenoviral vector transfer of PEDF.⁶⁹⁻⁷¹ A phase 1 trial of an adenoviral vector delivered intravitreal PEDF (AdPEDF) completed in 2006 showed stabilization of CNVM in wet AMD patients for up to 12 months.⁷²

TGF- β

Transforming growth factor- β 's exact role remains somewhat more elusive in angiogenesis. It is believed to be both pro- and antiangiogenic, depending on its concentration and surrounding environment. Low levels lead to angiogenesis by upregulating angiogenic factors and proteases. High levels stabilize basement membrane formation, recruit smooth muscle cells, and inhibit endothelial cell growth.⁷³ Ogata showed TGF- β levels remained elevated in photocoagulated RPE cells, while angiogenic factors, including VEGF and IL-8, were reduced.⁷⁴ In the context of cancer and tumor angiogenesis, Bernebeu describes TGF- β 's “dual and paradoxical role”; first it acts as a tumor suppressor in a premalignant stage, and then its role becomes “exploited” by active tumor cells to aid in its own growth. Tumor cells can become resistant to TGF- β via mutating TGF- β receptors, thus reacting as if in a low-level TGF- β environment.⁷⁵

Uveal Melanoma

Uveal melanoma cells are one of the few cell types that use a process coined “molecular mimicry” to enhance their microcirculation. Folberg and Maniotis found de novo vascular channels that were completely devoid of endothelial cells in aggressive melanoma cells.⁷⁶ This suggested tumor cell ability to form new circulatory channels independent of angiogenesis, hence discovering a potential new way to diagnose and treat tumor growth. In addition to this novel concept, angiogenesis also plays a role in uveal melanoma's growth. In 1979, Folkman implanted aqueous humor aspirated from eyes with uveal melanoma, eyes with retinoblastoma and control eyes into the chorioallantoic membrane of chick embryos. The majority of tumor-laden samples produced an angiogenic response in the chick embryo, while only one sample from a control eye did (this patient later developed lymphocytic leukemia).⁷⁷

Recent reports of VEGF expression in uveal melanoma have been highly variable. Generally, elevated VEGF levels have been seen in samples with a necrotic tumor component but do not appear to be related to tumor size or presence of metastases.⁷⁸⁻⁸⁰ This year, bevacizumab (Avastin, Genentech) and gene transfer of PEDF (an angiogenesis suppressor) decreased uveal melanoma growth and hepatic micrometastases in a mouse model.^{81,82}

DISCUSSION

In addition to the above factors, several other growth factors, cytokines and environmental conditions are involved in the normal and abnormal cascade of angiogenesis. As with any disease process, it is vital to understand the pathophysiology in order to better target treatments. With regard to the eye, preventing angiogenesis is multifactorial and complex. Despite our lack of full understanding of these diseases (eg, AMD), we have been able to halt or at least slow the progression of angiogenesis.

Laser photocoagulation has been the mainstay of treatment for retinal neovascularization. It has been used for CNV and then was replaced with photodynamic therapy, which in turn has been largely replaced by anti-VEGF injections. Currently, anti-VEGF treatment has taken center stage due to the primary role VEGF has in ocular neovascularization. In the past decade, tremendous advancements have been made in the treatment of wet AMD.

Newer anti-VEGF agents are under investigation, such as aflibercept (VEGF Trap-Eye, Regeneron). It has a longer duration of action compared to ranibizumab (Lucentis, Genentech) and thus may allow for a less frequent dosing schedule. There are also clinical trials evaluating small-interfering RNA and combination therapy with brachytherapy to address VEGF-induced angiogenesis.

Additionally, other targets of angiogenesis are under investigation, such as receptor tyrosine kinase inhibitors to target VEGF and PDGF receptors, complement modulators, MMP and UPA inhibitors, and even doxycycline. Recently, Cox showed that oral doxycycline, through its anti-inflammatory properties and MMP-suppression effects, reduced angiogenesis in CNVM and pterygium mouse models.⁵² For now, anti-VEGF agents are the mainstay for the treatment of choroidal angiogenesis. For retinal angiogenesis, such as in PDR, laser photocoagulation and/or anti-VEGF agents may be used.

CONCLUSIONS

A delicate balance must be struck between angiogenesis and its counterpart, angiostasis. Retinal neovascularization and CNV may ensue when this balance goes awry. Retinal neovascularization is usually initiated in hypoxic states (eg, PDR), whereas CNV is usually a result of aging, chronic inflammation and oxidative damage (eg, AMD). VEGF has been strongly implicated in both, but other contributing factors include complement, fibroblast growth factor, insulin-like growth factor 1, matrix metalloproteinase, urokinase, interleukin-8, tumor necrosis factor- α and pigment epithelium-derived growth factor.

Due to its enormous complexity, there are many pathways to target when treating ocular neovascularization. Although not a very elegant treatment, laser photocoagulation has been a successful treatment for retinal neovascularization. A bit more refined, targeting VEGF and its resulting molecular cascade of events has shown great hope in the treatment of both retinal and choroidal neovascularization. Potentially longer-lasting treatments that target more specific pathways may come about in the treatment of ocular neovascularization, thus reducing angiogenic-related eye disease and blindness. **RP**

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Table of Contents

Archives

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