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A LITERATURE REVIEW ON PATHOPHYSIOLOGY AND MODERN APPROACHES TO THE TREATMENT OF NEOVASCULAR EYE DISEASES

Authors: Sh.O.Abdullaev, G.N.Mamatkhujaeva, A.K.Abdullaev
Andijan State Medical Institute

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Abstract:

Neovascular pathology (NVD) in posterior segment the eye leads to visual deterioration or even loss in several ocular diseases. Proliferative diabetic retinopathy, neovascular age-related macular degeneration, and retinopathy of prematurity are predominant in the list of NVD. Together, these three diseases afflict persons in all stages of life from birth through late adulthood and account for most instances of legal blindness. Thus being aware of the origin, etiology and pathophysiology, clinical manifest and the modern approaches to the management and treatment of these diseases is substantial.

Keywords: Neovascular diseases, growth factor, intravitreal injections, diabetic retinopathy, neovascular age-related macular degeneration, retinopathy of prematurity

INTRODUCTION

Retinopathy of prematurity (ROP) occurs in premature neonates. Normally, the retina becomes completely vascularized at full term. In the premature baby, the retina remains incompletely vascularized at the time of birth. Rather than continuing in a normal fashion, vasculogenesis in the premature neonatal retina becomes disrupted. Abnormal new proliferating vessels develop at the juncture of vascularized and avascular retina. These abnormal new vessels grow from the retina into the vitreous, resulting in hemorrhage and tractional detachment of the retina. Although laser ablation of avascular peripheral retina may halt the neovascular process if delivered in a timely and sufficient manner, some premature babies nevertheless go on to develop retinal detachment. Surgical methods for treating ROP-related retinal detachments in neonates have limited success at this time because of unique problems associated with this surgery, such as the small size of the eyes and the extremely firm vitreoretinal attachments in neonates.

Diabetic retinopathy is the leading cause of blindness in adults of working age. In persons with diabetes mellitus, retinal capillary occlusions develop, creating areas of ischemic retina. Retinal ischemia serves as a stimulus for neovascular proliferations that originate from pre-existing retinal venules at the optic disk or elsewhere in the retina posterior to the equator. Severe visual loss in proliferative diabetic retinopathy (PDR) results from vitreous hemorrhage and tractional retinal detachment. Again, laser treatment (panretinal photocoagulation to ischemic retina) may arrest the progression of neovascular proliferations in this disease but only if delivered in a timely and sufficiently intense manner. Some diabetic patients, either from lack of ophthalmic care or despite adequate laser treatment, go on to sustain severe visual loss secondary to PDR. Vitrectomy surgery can reduce but not eliminate severe visual loss in this disease.

Age-related macular degeneration is the leading cause of severe visual loss in persons over 65 years old. In contrast to ROP and PDR, in which neovascularization emanates from the retinal vasculature and extends into the vitreous cavity, AMD is associated with neovascularization originating from the choroidal vasculature and extending into the subretinal space. Choroidal neovascularization causes severe visual loss in AMD patients because it occurs in the macula, the area of retina responsible for central vision. The stimuli which lead to choroidal neovascularization are not understood. Laser ablation of the choroidal neovascularization may stabilize vision in selected patients. However, only 10% to 15% of patients with neovascular AMD have lesions judged to be appropriate for laser photocoagulation according to current criteria. Retinopathy of prematurity, proliferative diabetic retinopathy, and neovascular age-related macular degeneration are but three of the ocular diseases which can produce visual loss secondary to neovascularization. Others include sickle cell retinopathy, retinal vein occlusion, and certain inflammatory diseases of the eye. These, however, account for a much smaller proportion of visual loss caused by ocular neovascularization. Additional treatments beyond laser photocoagulation and vitrectomy surgery are needed to improve outcomes in these patients. Pharmacological

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antiangiogenic therapy can potentially assist in prevention of the onset or progression of ocular neovascularization and is a current goal of many research laboratories and pharmaceutical companies [1].

Factors Affecting Vasculogenesis and Angiogenesis

Development of pharmacological strategies for treating ocular neovascularization depends on our gaining a more thorough understanding of the processes involved in vasculogenesis (generation of primitive embryonic blood vessels from mesodermal cells called angioblasts) and angiogenesis (development of new vessels from preexisting vessels) [2,3]. Studies on such seemingly diverse topics as wound healing, tumor growth and metastasis, embryological development, and ophthalmic disease have all contributed to our understanding of basic mechanisms involved in new vessel formation. Our current knowledge indicates that vasculogenesis and angiogenesis result from complex interactions between factors which either stimulate or inhibit endothelial cell differentiation, proliferation, migration, and maturation. Endothelial cells respond to regulatory proteins called growth factors that tend to be produced locally within the involved tissue and are secreted either by endothelial cells themselves or by neighboring cells. Counterbalancing the effects of endothelial growth factors are naturally occurring endogenous angiogenesis inhibitors. In addition to responding to these soluble stimulatory and inhibitory factors, endothelial cells interact with and respond to changes in the extracellular matrix through cell surface receptors called adhesion molecules. Research in each of these areas has suggested possible means of pharmacological manipulation of endothelial cell behavior.

Growth Factors

A variety of endothelial cell growth factors have been identified including fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), placental growth factor (PGF), insulin-like growth factor 1 (IGF-1), and platelet-derived endothelial cell growth factor (PD-ECGF).[4,5,6] Of these, the FGF and VEGF families and their cell surface receptors have been most fully characterized. Our emphasis will be on basic FGF (bFGF, also known as FGF-2) because this is the growth factor under study in the article by Ozaki and co-authors in this issue [7].

Fibroblast growth factor activity was discovered in 1940 when extracts from brain and pituitary were found to stimulate proliferation of cultured fibroblasts [8]. By the 1980s two forms of FGF, acidic FGF (aFGF) from brain and basic FGF (bFGF) from pituitary, had been purified using heparin-affinity chromatography [9]. Both forms (aFGF and bFGF) are single-chain proteins of approximately 140 amino acids. In addition to aFGF and bFGF, several other members of the FGF family now are known and a number of soluble and cell surface FGF receptors have been characterized [10,11]. Basic FGF is found in extracellular matrix (ECM) from which it can be released by ECM-degrading enzymes such as serine proteases and metalloproteases [12]. FGF receptors also have been localized in vascular extracellular matrix [13]. Fibroblast growth factors are produced by a variety of cell types in culture including vascular endothelial cells, fibroblasts, smooth muscle cells, astrocytes, granulosa cells, adrenocortical cells, and retinal pigment epithelial cells, as well as a large number of malignant cell types. Fibroblast growth factors also function during embryonic development and wound healing[14,15]. Many of the cells which produce FGF, including vascular endothelial cells, also respond to this growth factor. In vivo bFGF has angiogenic activity and is expressed in high levels by endothelial cells during tumor angiogenesis and vasculogenesis [16]. In vitro bFGF causes endothelial cell proliferation, protease production, and chemotaxis. In collagen matrices, bFGF enhances tube formation by endothelial cells [17]. An unusual feature of aFGF and bFGF molecules is the absence of a secretory signaling sequence typical of proteins secreted by the endoplasmic reticulum–Golgi apparatus [18]. Apparently, bFGF is released from cells by a different mechanism. Basic FGF is thought to exert both paracrine and autocrine influences on vascular endothelial cells. Paracrine angiogenic activity is illustrated by tumor angiogenesis where neoplastic cells which release bFGF form fast growing, highly vascularized tumors. Autocrine angiogenic activity has been demonstrated by experiments in which endogenously produced bFGF proved necessary for endothelial cell migration from a confluent monolayer into a denuded area of the culture plate from which a patch of cells was removed with a razor blade [19]. Release of bFGF by vascular endothelial cells also increases their production of plasminogen activator, yet another autocrine effect [20,21]. Therefore, tumor angiogenesis and other neovascular diseases may be initiated by stimuli which increase autocrine production of bFGF.

Endogenous Inhibitors of Angiogenesis

Growth factors which promote angiogenesis appear to be counterbalanced by endogenous compounds which inhibit angiogenesis. Examples of these natural inhibitors of angiogenesis include angiostatin, glioma-derived inhibitory factor, endostatin, and thrombospondin, which have been found in association with tumor-related angiogenesis [22,23]. One of these angiogenesis inhibitors also has been studied in relation to ocular disease, thrombospondin-1. Thrombospondins are a family of proteins present in platelet granules and

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secreted by several cell types including tumor cells [24].These proteins have varied effects on different cell types. Thrombospondins cause proliferation of fibroblasts and smooth muscle cells but inhibit proliferation of endothelial cells. There are at least five thrombospondins, of which thrombospondin-1 is most interesting with respect to endothelial cell function. Thrombospondin-1 is produced by vascular endothelial cells, fibroblasts, smooth muscle cells, lens epithelium, corneal endothelium, and other cell types [25,26]. Thrombospondin-1 has been located in surgical specimens of fibrovascular membranes in patients with proliferative diabetic retinopathy [27]. In vitro thrombospondin-1 inhibits endothelial cell proliferation and adhesion. In vivo it inhibits angiogenesis. Synthetic peptides containing sequences from thrombospondin-1 inhibit endothelial cell chemotaxis in response to Bfgf [28]. Both bFGF and PDGF induce increased expression of thrombospondin indicating interaction between positive and negative angiogenic stimuli.

In recent years, innovative methods of conservative treatment of retinopathy of the retina accompanied by neovascularization have been actively developed and implemented. Medications have become available to clinicians that can block vascular endothelial growth factor (VEGF), which is considered a key link in the process of neovascularization, as well as retinal vascular hyperfiltration. At the same time, the use of most of them, in combination with standard therapy, improves the long-term prognosis of the disease.

For the first time, VEGF was discussed in 1983 as a factor contributing to an increase in the vascular permeability of tumors. VEGF is a homodimeric glycoprotein and is structurally similar to platelet growth factor. It has the ability to bind to 5 types of receptors that have tyrosine kinase activity. It is known that most physiological and pathological processes are caused by disorders of the VEGF-VEGFR system, including embryogenesis, regulation of female reproductive function, pregnancy, wound healing, development of diabetic retinopathy, tumor growth, and ischemic diseases.

VEGF is also involved in the processes of early postnatal angiogenesis. In the adult vascular wall, VEGF exerts its influence on several levels: as a survival factor for endothelial cells, increases vascular permeability, and provides potent vasodilator properties. Glomerulogenesis and the functions of the renal glomerular filter in the kidneys are also under the gene-dependent strict control of VEGF.

In addition to physiological, VEGF also has other actions and effects that are triggered by some pathogenetic mechanisms, but are useful and include the ability to stimulate the formation of collateral circulation, which is necessary for the survival of cells exposed to hypoxia, as well as improving trophism in wound healing processes.

Today, anti-VEGF drugs have found use in the adjuvant treatment of metastatic tumors. VEGF inhibitors are monoclonal antibodies that can selectively bind to VEGF and block its action. Thanks to them, neoangiogenesis is suppressed in tumors, depriving neoplasms of the possibility of further growth. The data of recent studies in this direction made it possible to propose substances with anti-VEGF properties as one of the methods of conservative treatment of diabetic retinopathy. Due to this, a number of drugs that block the biological action of VEGF are available in modern clinical practice, these are: Pegaptanib (a drug-selective inhibitor of VEGF165), Bevacizumab and Ranibizumab (drugs that block any VEGF isoforms).

Pegaptanib, the main active ingredient in Macugen, from Eyetech Pharmaceuticals/Pfizer, is a polyethylene glycol-coupled neutralizing RNA aptamer that has the highest affinity (affinity and binding strength) for VEGF165. In rodent experiments, intravitreal administration of pegaptanib has been shown to significantly suppress leukostasis, retinal neovascularization, and VEGF-mediated cellular hyperfiltration. In the United States in 2004, the Food and Drug Administration (FDA) approved the use of pegaptanib in the treatment of wet age-related macular degeneration (AMD).

Ranibizumab, the main component of Genentech/Roche's Lucentis, is specifically designed to prevent the onset of neovascularization in AMD by altering the structure in rat long chain monoclonal antibodies. Unlike pegaptanib, ranibizumab is able to bind and inhibit the biological effect of any human VEGF isoform. In an experimental model of laser-induced choroidal neovascularization in non-human monkeys, intravitreal administration of ranibizumab blocked the formation of new vessels while simultaneously reducing the vascular permeability of existing vessels. In 2006, the FDA approved ranibizumab-based drugs for edematous wet AMD for use in the United States.

Bevacizumab, the active ingredient in Avastin, from Genentech/Roche, is made from anti-VEGF antibodies in laboratory mice. Like ranibizumab, it has the ability to bind all VEGF isoforms. Despite a small number of randomized trials, bevacizumab is used as an intravitreal injection for the treatment of neovascularization in wet AMD, however, this substance has not yet received official approval.

Data from clinical trials of anti-VEGF drugs

Systemic use as an intravenous infusion. Data are available from only one study of intravenous use of bevacizumab associated with ophthalmic pathology. This is the treatment of 18 patients suffering from neovascular AMD. In this uncontrolled study, the dose

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used was 5 mg/kg in 1, 2, and 3 injections given 2 weeks apart. The visual acuity of patients during the study increased already two weeks after the start of the drug administration and remained at the achieved level for 24 weeks of observation. By the end of the study, a significant decrease in the thickness of the retina was revealed. At the same time, only six treated patients received additional therapy during the observation period. Despite the impressive results of the study, it was not planned in order to identify a possible side effect.

Intravitreal administration. Sufficiently large-scale clinical studies have been conducted on the use of pegaptanib and ranibizumab in patients with AMD. Pegaptanib was found to be less effective than ranibizumab. However, its use is associated with lower risks of undesirable consequences. So, according to the results of three central studies using ranibizumab, data were obtained on an increase in the incidence of cardiovascular disorders, including strokes and bleeding, although this increase was not statistically significant.

Several studies have reported positive outcomes in the treatment of patients with diabetes mellitus. In a double-blind, prospective, controlled, multicentre, dose-dependent study that included 172 patients with diabetic macular edema, participants received pegaptanib and had a better prognosis for visual function by the end of the study (at 36 weeks). A decrease in the thickness of the central retina was found and fewer cases required additional laser treatment.

Currently, bevacizumab is used by many ophthalmologists around the world as a preoperative therapy for proliferative DR before vitrectomy.

Undesirable effects from the administration of VEGF inhibitors

Anti-VEGF drugs are injected into the vitreous body directly through the scleral puncture, but their penetration into the systemic circulation is still possible. In turn, this can lead to unwanted systemic manifestations. At the same time, hypertension and proteinuria can be considered as markers of the systemic effect of anti-VEGF drugs, which are detected especially often when the latter are used in the treatment of oncological diseases. An increase in blood pressure is a consequence of an increase in the level of peripheral vascular resistance due to the suppression of the production of nitric oxide by endothelial cells, the formation of which is stimulated by VEGF through the activation of NO synthase, but is also explained by a change in renal function. Other potential complications that have been observed as a result of the use of anti-VEGF include suppression of muscle tissue regeneration processes with myocardial remodeling, infertility, alteration of the wound healing process with the formation of collateral circulation, bleeding in the gastrointestinal tract.

Thus, the potential systemic effects of the use of VEGF inhibitors (including hypertension, proteinuria, impaired wound healing, collateral circulation, etc.) can be dangerous, especially in people with diabetes mellitus.

Among the ophthalmic manifestations of anti-VEGF drugs, it is worth noting endophthalmitis, lens damage and retinal detachment as the most frequently reported. Serious complications arising in response to intraocular injections of drugs are quite rare. At the same time, the cumulative risk is much higher in people with diabetes who require repeated treatment for many years.

In addition to the side effects from the intravitreal injection itself, there are other potential unwanted effects, the development of which is due to the suppression of the action of VEGF. It should be noted that VEGF formed by retinal pigment cells provides the functions of choriocapillaries and has a neuroprotective effect in retinal ischemia. Interestingly, when pegaptanib, which is unable to bind to VEGF120 (or human VEGF121), was used to suppress VEGF, there was no reduction in the number of retinal ganglion cells. Very often, with intravitreal administration of bevacizumab (which blocks any known form of VEGF), no toxic effect on retinal ganglion cells is observed. However, it should be noted that so far there has been no evidence of its damaging effects on the retina, which could be detected by light microscopy. Nevertheless, mitochondrial destruction of the internal segments of photoreceptors (identified by electron microscopy), as well as increased apoptosis, was noted.

CONCLUSION

The intravitreal method of introducing anti-VEGF drug solutions is used as an effective way to deliver the drug directly to the retina. According to preliminary results, the treatment of patients with DME, AMD, as well as proliferative DR gave very encouraging and convincing results. However, intravitreal injections are invasive procedures and are associated with a potential risk of bleeding, endophthalmitis, and retinal detachment.

Anti-VEGF agents: pegaptanib, ranibizumab, bevacizumab, are currently available as ophthalmic drugs. So far, their use is only an addition to traditional treatment. Their use improves the prognosis of treatment, reduces the need for laser coagulation of the retina. Provides an opportunity to carry out preoperative preparation of vitretomy or antiglaucoma surgery, as well as reduce the risk of potential postoperative complications.

However, any long-term treatment that can increase the progression of cardiovascular disorders requires additional clinical studies that are aimed not at identifying positive effects, but at clarifying the risk of

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developing systemic complications, especially for patients with diabetes mellitus.

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