ANTIANGIOGENIC DRUGS USED FOR THE TREATMENT OF EYE DISEASES

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Abstract: *After countless recent studies, the introduction of therapy with anti-VEGF agents in ophthalmology has been revolutionizing the therapeutic management of exudative and vascular proliferative diseases. Currently, injections with anti-VEGF agents are part of the first course of treatment in age-related macular degeneration (AMD), diabetic macular edema (DME) and retinal vein occlusion (RVO). Also, they are considered as part of adjunctive therapy in ophthalmic diseases like proliferative diabetic retinopathy (PDR) and neovascular glaucoma (NVG). Antiangiogenic agents have been used successfully in the treatment of rare diseases as: sickle cell retinopathy, retinopathy of prematurity, radiation retinopathy and other vascular diseases proliferative. In any case, the safety and potential toxicity of this long-term therapy need to be monitored in the future.*

INTRODUCTION

Angiogenesis means formation of new blood vessels from preexisting blood vessels. The term was first used by Hertig in 1935 related to neovascularization in the placenta. New blood vessel formation occurs under a lot of physiologic and pathologic conditions.(1)

Physiologic angiogenesis can be found in reproduction and development, as well as in wound healing. Pathologic angiogenesis plays an essential part in tumour growth, in certain chronic inflammatory conditions, such as rheumatoid arthritis and in ocular neovascularizing diseases.

In the eye, angiogenesis is pathogenetically responsible for common vision-threatening diseases, such as proliferative diabetic retinopathy, retinopathy of prematurity, rubeosisiridis and secondary glaucoma after branch and central retinal vein occlusion, age-related maculopathy and corneal neovascularization. Although inhibition of angiogenesis in cancer therapy was already suggested by Folkman in 1971, only the recent progress in understanding the process and the regulation of angiogenesis has made this therapeutic option a realistic one.(2)

The process of angiogenesis

In the adult, new blood vessels arise by sprouting from preexisting vessels. This process can simply be separated in three steps.

1. Angiogenic activation of endothelial cells and degradation of basement membrane. Angiogenic factors like vascular endothelial growth factor (VEGF) induce an angiogenic, activated state of the endothelial cells lining the blood vessel. These activated cells then secrete proteases which degrade the underlying basement membrane and the surrounding extracellular matrix (e.g. plasminogen activator factor).

2. Endothelial proliferation and migration. Angiogenic factors like VEGF are mitogens specific for endothelial cells, which in response proliferate and migrate in direction of the angiogenic stimulus out of the preexisting blood vessel.

3. New vessel formation. Outgrowing endothelial cells degrade extracellular matrix in their surrounding. On the other hand, they need certain extracellular matrix (ECM) proteins to adhere at.

These adhesion proteins vary depending on the angiogenic factor which stimulates the endothelial cell: VEGF induces expression of the integrin a $_{Vb\ 5}$, which binds to the ECM-protein vitronectin, fibroblast growth factor (FGF) for example induces the expression of the integrin a $_{Vb\ 3}$. This is of special interest because pharmacological blockade of these binding proteins can inhibit endothelial cell attachment to the ECM and induce apoptosis (programmed cell death) of the outgrowing endothelial cells.

Endothelial cells then arrange to form a new lumen and eventually fuse with another blood vessel and circulation is established. Other cells of the vessel wall, like pericytes or smooth muscle cells follow.(3)

Pericytes are important because they stabilize the vessel wall and seem to maintain endothelial cells (EC) in a quiescent, antiangiogenic state. At least, in vitro they secrete the antiangiogenic factor TGF b when cocultured with ECs.

VEGF appears to be the most important angiogenic factor because is responsible mainly for eye diseases like: proliferative diabetic retinopathy, central retinal vein occlusion, irianarubeosis.

A moderate role belongs to other angiogenic factors as: angiopoietin, erythropoietin basic fibroblast growth factor (bFGF), insulin like growth factor (IGF), protein kinase C (PKC) enzyme.

VEGF-A human gene is organized into 8 exons separated by 7 introns.

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VEGF is associated with barrier rupture of blood - retina and increased vascular permeability of retinal vessels.

Currently, there are 4 inhibitors agents of VEGF that are used in the treatment of proliferative retinal diseases: Pegaptanib, Bevacizumab, Ranibizumab, VEGF Trap.

- Pegaptanib is a pegylated ribonucleic acid that binds with high affinity to VEGF165.
- Bevacizumab is similar to an antibody synthesis anti VEGF-A, and can block all its forms; it was initially used in the treatment of metastatic colon cancer and then in other cancers.

Inhibition of the angiogenic factor VEGF

There are four potential targets for inhibition of the angiogenic factor VEGF. Inhibition of VEGF will not only result in the inhibition of the angiogenic property of VEGF but it will also interfere with the permeability increasing effect of VEGF.

This could be especially interesting in inflammatory diseases with breakdown of the blood retina barrier associated with angiogenesis.

1. *Inhibition of VEGF-secretion*. Intravitreal injection of antisense oligonucleotides against VEGF could reduce VEGF production and angiogenesis in an animal model with hypoxic retina. Antisense oligonucleotides interfere with VEGF production by binding to VEGF mRNA and inhibiting translation of mRNA into a protein. Also, pharmacological alterations of the haem-proteins responsible for the oxygen sensing mechanisms related to VEGF secretion could interfere with VEGF release.
2. *Inactivation of VEGF*. Adamis could demonstrate the feasibility of this approach in an animal model where the intravitreal injection of neutralizing VEGF-antibodies minimized the rubeosisiridis usually occurring after experimental induction of central retinal vein occlusion.
3. *Blockade of VEGF receptors on ocular endothelial cells* e.g. with TBC 1465 and TBC 1466. This "strategy" is also part of the natural antiangiogenicsystem. Soluble receptors for VEGF and FGF circulate in the blood stream binding to and inactivating circulating angiogenic factors. In addition, heterodimers of VEGF, which display a 20-50 fold less mitogenic activity than "normal" VEGF for endothelial cells in vitro, were found.
4. *Inhibition of postsynaptic VEGF induced cell activation*. VEGF receptors are tyrosine kinase receptors, whose intracellular effect is mediated by phosphorylation events. Tyrosine kinase inhibitors as Lavendustin A can interfere with this effect.

Regarding antiangiogenic therapy by inhibition of angiogenic factors, some general principles for this special approach shall be discussed.

First, that probably not a single angiogenic factors alone is responsible for pathologic angiogenesis in a definite disease. This implies that a cocktail of antiangiogenic factors will probably be necessary to achieve sufficient inhibition of angiogenesis.

Second, that the "orchestra" of angiogenic factors probably varies between different organs and different pathologic entities. This means that the antiangiogenic cocktail will vary for different ocular neovascularizing diseases, e.g. a different set of antiangiogenic factors will be used for proliferative diabetic retinopathy than for corneal neovascularization after herpetic keratitis.

Table no. 1. Angiogenic and antiangiogenic factors

Angiogenic factors	Antiangiogenic factors
aFGF, bFGF	Angiostatin
VEGF/VPF	PF IV
Angiogenin	TIMP 1,2,3
TGF a , TGF b	Prolactin
TNF a	Interferon a
PD-ECGF	TGF b
Placenta growth factor	Protamin
Interleukin 8	Steroids
HGF	Thrombospondin 1,2,3
Proliferin	
GM-CSF	
Angiotropin	
E-Selectin, VCAM-1, CD 44	
Prostaglandines PGE_1, PGE_2	

The use of antiangiogenic drugs in eye diseases

Age-Related Macular Degeneration (AMD)

There are two types of AMD: Non neovascular and neovascular.

Non-neovascular form is characterized by the presence of hard and soft drusen and changes in the retinal pigmented epithelium (RPE).(6)

Neovascular form is characterized by the presence of choroidalneovascular membrane (CNVM) that has usually associated subretinal fluid, hemorrhage and possibly subretinal fibrosis with central vision loss.(7)

In the past, laser photocoagulation was used for vision loss. Photodynamic therapy was another option - combines photosensitive agents and low energy laser.(8)

A dramatic advance was the introduction of antiangiogenetics factors that not only reduce the incidence of vision decrease but even improve it.(9)

Choroidal neovascularization in other diseases

CNVM also occur in other diseases: pathological myopia, angioide tread, ocular histoplasmosis and traumatic choroidal rupture.(10,11)

Diabetic retinopathy and macular edema

Vision loss in diabetic retinopathy is the leading cause of complications through neovascularization in proliferative retinopathy or exudation of macular edema.(12)

Photocoagulation laser remained standard complications for 25 years. Regarding anti VEGF therapy in the treatment of macular edema can say that the rate of vision improvement is almost double compared to laser therapy.(13,14,15,16)

Antiangiogenic agents as an adjunct to vitrectomy

Bevacizumab has shown some benefit as adjuvant prioritized vitrectomy in patients with PDR.Prospective and retrospective studies have suggested that preoperative Bevacizumab injection decreases intraoperative bleeding and postoperative hemorrhage vitreous.(17)

Antiangiogenic agents in neovascular glaucoma

Bevacizumab was actually introduced in the

therapeutic management of neovascular iris (NVI) and neovascular glaucoma (NVG). VEGF agents are very efficient inducing rapid regression of neovascularization ischemia but the effect is temporary requiring other additional treatments (such as laser photocoagulation or develop therapeutic molecules mechanisms that act in time and can be administered quickly).(18)

Antiangiogenic treatment for retinal vein occlusion

It is the second retinal vascular cause of vision loss.

Central retinal vein obstruction ischemic form is often accompanied by macular edema, retinal and retinal neovascularization.(19)

Ischemia induces the production of various cytokines that lead to the formation of neovessels with increased capillary permeability.

VEGF and IL6 have been found in high concentrations in patients with central retinal vein obstruction.

CONCLUSIONS

Currently, there are being conducted studies related to angiogenic factors and their role in the human body.

Recent discoveries help us treat certain diseases that had practically no successful therapy.

The role of the antiangiogenic treatment is curative and adjuvant in other therapies.

In ophthalmology, in the last 5 years, this treatment has practically represented a revolution in the therapeutic management of retinal disease and not only.

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