Review Article

Anti-VEGF therapy in ophthalmology

ABSTRACT

Angiogenesis is that process in which growth of new blood vessels occurs from the pre-existing vasculature, occurring in both healthy and pathological conditions. Usually there is a balance maintained between angiogenesis regulators (angiogenesis promoting factors and angiogenesis inhibiting factors) but when this balance is lost, there is either too much or too little angiogenesis.
VEGF (Vascular endothelial growth factor) and it's receptor (VEGFR) are key regulators of angiogenesis which promote it.
It has been seen that, it plays a major role in the mechanism of regeneration of blood vessels, inflammation of body tissues, cancer states and wound healing.
There are various pathological conditions which show increased VEGF activity.
Nowadays, there has been increased use of anti-VEGF drugs which targets the vascular endothelial growth factor and slow downs it's action and application of this therapy in ophthalmology is also becoming wider and wider.
The implications of anti-VEGF dungs are cancers, rheumatological disorders, macular oedema, various retinopathies, glaucoma etc.
Anti-VEGF treatment comprises of three main drugs, namely- Avastin, Lucentis and Eylea. The efficiency of all of them have been proven to be equal with varying manufacturing costs, packaging and associated risks.
These are the brand names for bevacizumab, ranibizumab, aflibercept respectively which has helped us to achieve different milestones in treating all kinds of retinal diseases.
Several other diseases like iris neovascularisation, age related macular degeneration (AMD), corneal diseases also have been treated using anti-VEGF drugs.
Like all drugs, anti-VEGF drugs also have some limitations and side effects including short half-life, systemic side effects therefore the development of new drugs still goes on.

KEYWORDS

Angiogenesis; VEGF; VEGFR; anti-VEGF therapy; macular oedema; AMD; bevacizumab; ranibizumab; aflibercept.

INTRODUCTION

Angiogenesis is derived from a Greek word “Angelon” meaning vessel, formation of blood vessels from the existing vasculature. It can be both a physiological or a pathological process, by which there is formation of new blood vessels in the body. It is an inevitable process which occurs throughout the life. This process involves the migration and differentiation of endothelial cells which line the inside wall of blood vessels (1).

In organs like heart, skeletal muscle, brain and other tissues where the primary function of blood vessels is to supply nutrients in adequate amount as per the need, all the vessels grow and revert back to normal according to the metabolic needs of the tissues. The key factor affecting angiogenesis is Oxygen. Therefore, angiogenesis is necessary for oxygen and nutrient delivery to tissue and hypoxia is a major determinant of angiogenesis (2).

The significance of vasculature (capillaries) is to provide nutrition to the tissues and fulfil the metabolic requirements of the body. For instance, during exercise the increased metabolic activity leads to the expansion of blood vessels present in the skeletal muscle, thus fulfilling the increased oxygen demand of the body. Chronic stimulation of a motor nerve to a glycolytic muscle at a slow frequency characteristic of oxidative muscle converts glycolytic fibres to oxidative fibres and causes extensive angiogenesis as well as growth of all arteries and veins (3).

On the other hand, in pathological conditions such as cancer, there is proliferation of cells and bodily tissues hence promoting angiogenesis. There are many more conditions in which this phenomenon is seen such as macular degeneration, severe diabetic retinopathy, macular oedema, vascular occlusion, glaucoma, vitreous haemorrhage etc.

OBJECTIVES

a. To learn about the mechanism of angiogenesis and how VEGF acts.

b. To learn about the classification and mechanism of action of anti-VEGF drugs

c. To know about important indications of the use of anti-VEGF drugs in ophthalmology

d. To learn about some of the important drugs used in certain conditions.

e. To understand the contraindications of anti-VEGF drugs.

f. To understand the complications that these drugs can cause.

MECHANISM OF ANGIOGENESIS

As we said above that angiogenesis is that process which results in newly formed blood vessels. The activity of angiogenesis is maintained by an equilibrium between the factors that stimulate and inhibit it.

But what these factors are really?

There is a signalling system which mainly modulates the proliferation and movement of endothelial cells that form the basis of any vessel, it is called Vascular endothelial growth factors (VEGF) and its receptors.

VEGF: It has a mitogenic and an anti-apoptotic effect on endothelial cells by increasing the vascular permeability and promoting cell migration. By these processes it regulates angiogenesis. The VEGF family is composed of several members: VEGF-A (has different isoforms), VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, placental growth factor (PIGF) and recently added endocrine gland derived VEGF (EG-VEGF) (4).

For the formation of embryonic vascular system, a signalling system is required and is also dependent on VEGF.
Angiogenesis occurring in pathological conditions is also correlated with the stimulation of this signalling system.
Be it either any physiological condition or a pathological condition, ischaemia or hypoxia can directly or indirectly stimulate the "proangiogenic factors" and its receptors. There are many factors that are involved in this process and are as following-

a. VEGF A and its receptors – VEGRF1; VEGRF2
b. Placental growth factor

c. Transforming growth factor (beta)

d. fibroblast growth factor

2. Hypoxia inducible factor-1 (abbreviated as HIF-1) regulates the VEGF-A via VEGFR1 which itself is oxygen dependent for being regulated.

Proangiogenic factors are not the only ones that can be regulated by hypoxia since there are anti-angiogenic factors that are stimulated by a hypoxic environment such as:
a. thrombospondin-1

b. endostatin

It is important to note that, angiogenesis due to hypoxic environment is not an irreversible process as it can reverse on removal of the hypoxic stimulus and when the normal conditions are restored and the homeostasis is again maintained.

However, we'll talk about what happens after angiogenesis is induced to due to oxygen-less environment. Now, that angiogenesis has taken place the vascularity is bound to increase as the oxygen demand in the affected area rises up. So, to counter that oxygen demand neovascularisation occurs and increase in capillary surface, decreased diffusion of gases in the blood and adequate supply of blood in the body.

Now, when a regulation cycle has positive feedback, negative feedback also always exists in the nature. So, when the oxygen demands of the body have been met, both pro and anti – angiogenic factors return back to an optimum level and these signals ultimately stop the furthermore development of blood vessels.

Basically, this mechanism is directly related to the increased or decreased metabolic activity of the body.

A nucleoside, named, adenosine also plays a role in this. Hypoxic tissues produce adenosine from ATP which further returns the balance between oxygen demand and oxygen supply (3).

It should be noted that only VEGF-A is involved in angiogenesis. Action of VEGF-B is almost nil in this.

ANTI-VEGF DRUGS

Nowadays, an increased use of anti-VEGF drugs/ VEGF or VEGFR inhibitors has been witnessed. One can say it is an era of these drugs. While research is still going, following are the things that we know at the moment about them.

Some of the drugs that we know of are-

- Bevacizumab
- Ranibizumab
- Aflibercept
- Pegaptanib
- Lapatinib
- Sunitinib

Out of the these, the most broadly used are the first two that is, Bevacizumab and Ranibizumab and Aflibercept.

Ranibizumab is an FDA approved drug and bevacizumab is an off-label drug but cost efficient thus, making it ideal for use (5).

Table 1. ANTI-VEGF DRUGS

Bevacizumab	Ranibizumab
Sold under the brand name - AVASTIN	Sold under the brand name - LUCENTIS
Full sized antibody	Fragmented antibody
148 kilodaltons	48 kilodaltons
Clearance is slow	Clearance is 100 times faster
It has a long action but less dosage required.	It has approx. 150 times higher affinity
It costs less.	Costly
Has a half-life of approximately 18 days	Has a half-life of approximately 2-3 days.

Now, let's see how these drugs actually work in the body:

These drugs after entering the body, bind selectively to the free circulating VEGF so as to inhibit it's binding to the corresponding receptor that is VEGFR. This action of the drug ultimately causes reduction in growth of the vasculature.

Whenever the intake of drugs is stopped, angiogenesis resumes and again starts to form new vessels.

INDICATIONS OF ANTI-VEGF DRUGS

As of today, there are many conditions in which these drugs are being used immensely.

Cancer, be it any kind of cancer, is the most common indication for the use of anti-VEGF drugs. As the tumour grows, it's nutrients and oxygen requirements also increase till the point that it reaches a hypoxic state thus, stimulating angiogenesis. Anti-VEGF drugs block this process and regress the size of tumour.

It has also a wide variety of indications in ophthalmologic disorders like wet age-related macular degeneration (wet ARMD), Choroidal neovascular membranes, severe diabetic

retinopathy, vascular occlusions, glaucoma, vitreous haemorrhage, macular oedema, and some ocular tumours such as retinoblastoma etc.

MACULAR DEGENERATION

Specifically, wet age-related macular degeneration is a disorder in which the patient experiences severe loss of vision. Secondary to this, neovascularisation is also partly responsible for the said vision loss. It is obvious the aim is to bring improvement in the eyesight of the patient by using these drugs.

Studies have shown that patients on anti-VEGF therapy showed improvement in visual acuity by 15 or more letters. It may also be found in a follow up one year later that vision has improved to around 20/200 or better (5-8).
Any of the drugs can be used from these three- bevacizumab, ranibizumab and aflibercept. These are given as an injection intravitreally.
Monthly treatments until the drying of macula and slowly increasing time between applications can provide stable visual acuity to a patient.
In some patients, adverse effects are seen like inflammation in the eye or raised intraocular pressure being the most important. Others which may occur in small percentage includes vitreous haemorrhage, retinal detachment, myocardial infarction (systemic effect) etc.

DIABETIC RETINOPATHY

It is a very common and seriously life-threatening complication seen in the patients of diabetes. For so many years, it was being treated by a procedure called laser photocoagulation but as its name suggests using a laser can be a quite destructive process and may damage the retina further. Earlier steroids injections were also given intraocularly.
After conduction of so many trials, it came to light that anti-VEGF drugs are preservative in nature as compared to the use of laser and vision was also improved after its use. Patients who were administered anti-VEGF drug showed ~47% improvement in vision as compared to laser therapy which showed only ~19% improvement thus proving that anti-VEGF drugs are almost two times more efficient than laser therapy.
In this also, the preferred route is intravitreal.
Sometimes, both laser therapy and anti-VEGF therapies are combined and have resulted in a good outcome.

NEOVASCULAR GLAUCOMA

It is a secondary type of glaucoma and also a common indication of anti-VEGF drug use.
Anti-glaucoma drugs are available but use of anti-VEGF drugs has also shown very promising results by reducing the neovascular vessels and bringing down the intraocular pressure within ~48 hours of administration of intravitreal injection (mostly bevacizumab).
Earlier photocoagulation was also done as a part of treatment but now, combined treatment including photocoagulation and anti-VEGF drugs have shown better outcomes as compared photocoagulation alone.

OCULAR TUMOURS

It can be a retinoblastoma, retinal artery hemangioblastoma or some other tumour.
In all these cases, combination of anti-VEGF drugs along with chemotherapy and other available cancer treatments have shown good results in improving vision of the patient.

CONTRAINDICATIONS OF ANTI-VEGF DRUGS

These drugs are highly contraindicated in the following-

- If there is fibrovascular proliferation which may threaten the macula
- A patient with uncontrolled hypertension
- If the patient has known hypersensitivity to drugs
- If the patient has any type of active inflammation in the eye or around the eye.
- Patient with a cardiovascular disease.
- These drugs are also contraindicated in pregnant women and women who are lactating
- Contraindicated in children in pre-adolescent age.[8-13]

As it can be very harmful for patients, who fall under the above-mentioned categories, to take anti-VEGF drugs so the doctor should be extra careful while taking history thus, avoiding the occurrence of any mishappenings.

COMPLICATIONS/ADVERSE EFFECTS OF ANTI-VEGF THERAPY

No matter how good a drug is, there are always some complications or adverse effects present. Although they are only experienced by some percentage of the patients but sometimes can be quite severe.

These may include-

- Most commonly seen is the increase in intraocular pressure
- Endophthalmitis is the most devastating adverse effect, caused most frequently by streptococcus. Its occurrence ranges between 0.02-1.6%.
- In patients with macular oedema, there maybe recurrence even after the use of anti-VEGF drugs – Rebound macular oedema.
- There may be retinal detachment
- Hypertension is also seen.
- Cataract
- Inhibition of VEGF may stop cardiac remodelling and regeneration of skeletal muscle.
- Women may experience infertility in rare cases
- Stoppage in bone growth may also be seen.

Patients suffering from diabetes may have some worrisome adverse effects such as-
Delayed healing of the wound, hypertension, proteinuria, problem in the development of a collateral vessel etc.

MATERIALS AND METHODS

PubMed and google search engine were used to search the following key terms- "angiogenesis", "VEGF", "effect of metabolic activity on angiogenesis", "anti-VEGF drugs", "using anti-VEGF drugs in ocular disorders", "bevacizumab", "ranibizumab",
"Contraindications of anti-VEGF therapy", "adverse effects of anti-VEGF drugs" and from the results of these searches, articles were selected and used for writing this review. Tools from Microsoft word were also used to create the tables and other illustrations.

Discussion

angiogenesis is an inevitable phenomenon occurring in both healthy and pathological scenarios resulting in newly formed blood vessels.
In normal conditions, an equilibrium is maintained between pro-angiogenic factors and anti-angiogenic factors which are responsible for the regulation of angiogenesis.

And VEGF-A and its receptors play a massive role in this process.

The list of conditions in which angiogenesis occurs is never ending but they broadly be divided into – physiological angiogenesis and pathological angiogenesis. Physiological angiogenesis usually includes when a person is doing strenuous physical exercise, low oxygen availability and high oxygen demand (hypoxic environment) leads to the stimulation of angiogenesis.
Similarly in cancers, there is increased demand for oxygen and other essential nutrients for the growing tumour, ultimately resulting in neovascularisation.
So basically, it can be said that change in the metabolic activity of the body also affects the rate of angiogenesis. But it should be noted that is a reversible process which means when metabolic activity of the body reverts back to normal, angiogenesis also does the same.
Other pathological conditions (limited to ophthalmology) in which this can also be witnessed are, such as - retinopathies, macular oedema, macular degeneration, glaucoma, haemorrhage in vitreous, diabetic retinopathy, ocular tumours like retinoblastoma, haemangioma etc.

Angiogenesis is controlled by a signalling system comprising of positive feedback and negative feedback which work in a loop. When there is an increase in demand, blood vessels expand themselves, forming new vasculature and thus, compensating the demand by supplying adequate blood, oxygen and various other nutrients (POSITIVE FEEDBACK). Once this demand has been fulfilled, normal levels of proangiogenic and anti-angiogenic factors are once again attained and thus, putting a stop to this process (NEGATIVE FEEDBACK).
Above we saw that, adenosine also plays a role in this.

As we know, anti-VEGF therapy includes various drugs but there are only 3 drugs are that are used most widely, these are ranibizumab, bevacizumab and aflibercept.
These drugs act by blocking the action of VEGF by restraining it from binding with its receptor (VEGFR). This prevents further occurrence of angiogenesis. Whenever a person stops taking drugs, angiogenesis continues again.

These drugs have shown remarkable results in various diseases and therefore, their use has increased in the past few years.

Research is still going as there are many things that we still don't know about.

Contraindications of anti-VEGF drugs include: fibrovascular proliferation which may threaten the macula, uncontrolled hypertension, know hypersensitivity to drugs, inflammation in ocular or periocular area, any cardiovascular disease, pregnant and lactating women and pre-pubescent children.

Complications or adverse effects of these drugs can be as follows- rebound macular oedema, hypertension, retinal detachment, inhibition of cardiac remodelling and skeletal muscle regeneration, infertility in women, inhibition of bone growth etc. Diabetic patients specifically may face problems like proteinuria, hypertension, delayed wound healing, and problems in the development of a collateral vessel.

Conclusion:

In conclusion, anti-VEGF therapy represents advancement of the modern-day medicine. Anti-VEGF treatments have a huge impact on serious disorders which represent a large proportion of irreversible vision loss (5). This treatment improves vision in about one out of three people who take it and for a vast majority (nine out of ten), it at least stabilizes it.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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