Journal of Pharmaceutical Research International

33(61B): 91-97, 2021; Article no.JPRI.80329
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Anti-VEGF Therapy in Ophthalmology

Aanchal Sharma [a*] and Shashank Banait [b]

[a] Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha, India.
[b] Department of Ophthalmology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha, India.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i61B35139

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/80329

Review Article

Received 24 October 2021
Accepted 27 December 2021
Published 28 December 2021

ABSTRACT

Angiogenesis is when the 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 its receptor (VEGFR) are critical regulators of angiogenesis that promote it.It has been seen that it plays a significant role in the regeneration mechanism of blood vessels, inflammation of body tissues, cancer states, and wound healing. Various pathological conditions show increased VEGF activity.Nowadays, there has been increased use of anti-VEGF drugs, which target the vascular endothelial growth factor and slow down its action. The application of this therapy in ophthalmology is also becoming wider and wider. The implications of anti-VEGF dungs are cancers, rheumatological disorders, macular edema, various retinopathies, glaucoma, etc.

Anti-VEGF treatment comprises of three main drugs, namely-Avastin, Lucentis, and Eylea. Their efficiency has been proven to be equal with varying manufacturing costs, packaging, and associated risks.These are the brand names for bevacizumab, ranibizumab, aflibercept, respectively, which have helped us achieve different milestones in treating all kinds of retinal diseases.

Several other diseases like iris neovascularization, 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.

**Corresponding author: E-mail: aanchal.sharma607@gmail.com;*

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

1. INTRODUCTION

Angiogenesis is derived from the 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 new blood vessels are formed in the body. It is an inevitable process that occurs throughout life. This process involves the migration and differentiation of endothelial cells, which line the inside wall of blood vessels [1].

In organs like the heart, skeletal muscle, brain, and other tissues, where the primary function of blood vessels is to supply nutrients in adequate amounts as per the need, all the vessels grow and revert to standard according to the metabolic needs of the tissues. The critical factor affecting angiogenesis is Oxygen. Therefore, angiogenesis is necessary for tissue oxygen and nutrient delivery, and hypoxia is a significant determinant of angiogenesis [2].

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

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

1.1 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 essential indications of the use of anti-VEGF drugs in ophthalmology
d. To learn about some of the essential drugs used in certain conditions.
e. To understand the contraindications of anti-VEGF drugs.
f. To understand the complications that these drugs can cause.

1.2 Mechanism of Angiogenesis

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

But what are these factors?

A signaling system mainly modulates endothelial cells' proliferation and movement that form the basis of any vessel; it is called Vascular endothelial growth factors (VEGF) and its receptors.

1.3 VEGF

It has a mitogenic and an anti-apoptotic effect on endothelial cells by increasing 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 the embryonic vascular system, a signaling system is required and is also dependent on VEGF.

Angiogenesis occurring in pathological conditions is also correlated with the stimulation of this signaling system.

Be it either any physiological condition or a pathological condition, ischemia or hypoxia can directly or indirectly stimulate the "proangiogenic factors" and their receptors. Many factors are involved in this process and are as follows-

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 a hypoxic environment is not an irreversible process as it can reverse on the removal of the hypoxic stimulus and when the normal conditions are restored, and the homeostasis is again maintained.

However, we'll discuss what happens after an oxygen-less environment induces angiogenesis. Now that angiogenesis has taken place, the vascularity is bound to increase as the oxygen demand in the affected area rises. 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.

When a regulation cycle has positive feedback, negative feedback also always exists. So, when the body's oxygen demands have been met, both pro and anti-angiogenic factors return to an optimum level, and these signals ultimately stop the further development of blood vessels.

This mechanism is directly related to the body's increased or decreased metabolic activity.

A nucleoside named adenosine also plays a role in this. Hypoxic tissues produce adenosine from ATP, which further balances oxygen demand and supply [3].

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

1.4 Anti-vegf Drugs

Nowadays, 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 on, the 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 these, the most broadly used are the first two, 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].

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

After entering the body, these drugs bind selectively to the free circulating VEGF to inhibit its binding to the corresponding receptor that is VEGFR. This action of the drug ultimately causes a reduction in the growth of the vasculature.

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

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 prolonged action, but less dosage is required.	It has approx. 150 times higher affinity
It costs less.	Costly
It has a half-life of approximately 18 days.	Has a half-life of approximately 2-3 days.

1.5 Indications of Anti-vegf Drugs

Today, there are many conditions in which these drugs are being used immensely.

Cancer, be it any cancer, is the most common indication for the use of anti-VEGF tumors. As the tumor grows, its nutrients and oxygen requirements increase until it reaches a hypoxic state, thus stimulating angiogenesis. Anti-VEGF drugs block this process and regress the size of the tumor [6].

It also has 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 hemorrhage, macular edema, and some ocular tumors such as retinoblastoma, etc.

1.6 Macular Degeneration

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

Studies have shown that patients on anti-VEGF therapy showed improved 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 [5-9].

Any drugs can be used from these three- bevacizumab, ranibizumab, and aflibercept. These are given as an injection intravitreally.

Monthly treatments until the drying of the 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 that may occur in a small percentage include vitreous hemorrhage, retinal detachment, myocardial infarction (systemic effect), etc.

1.7 Diabetic Retinopathy

It is a severe and prevalent life-threatening complication seen in patients with 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 pretty destructive process and may damage the retina further. Earlier steroids injections were also given intraocularly.

After conducting so many trials, it came to light that anti-VEGF drugs are preservative compared to the use of laser, and vision was also improved after its use. Patients who were administered anti-VEGF drugs showed ~47% improvement in vision 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, resulting in a good outcome.

1.8 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 anti-VEGF drugs have 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.

1.9 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.

1.10 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 cardiovascular disease.
- These drugs are also contraindicated in pregnant women and women who are lactating
- Contraindicated in children in pre-adolescent age [9-14].

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

1.11 Complications/Adverse Effects of Anti-vegf Therapy

No matter how good a drug is, there are always some complications or adverse effects. However, they are only experienced by some percentage of the patients but sometimes can be pretty 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%.
- There may be recurrence in patients with macular edema even after using anti-VEGF drugs – Rebound macular edema.
- There may be retinal detachment
- Hypertension is also seen.
- Cataract
- Inhibition of VEGF may stop cardiac remodeling and regeneration of skeletal muscle.
- Women may experience infertility in rare cases
- Stoppage in bone growth may also be seen.

Patients who have diabetes may have some problematic adverse effects such as-
Delayed healing of the wound, hypertension, proteinuria, problems in developing a collateral vessel, etc.

2. MATERIALS AND METHODS

PubMed and Google search engine was 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. Microsoft Word tools were also used to create the tables and other illustrations.

3. DISCUSSION

Angiogenesis is an inevitable phenomenon occurring in 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 are broadly divided into physiological and pathological. Physiological angiogenesis usually includes when a person is doing strenuous physical exercise, low oxygen availability and high oxygen demand (hypoxic environment) lead to the stimulation of angiogenesis.

Similarly, there is increased demand for oxygen and other essential nutrients for the growing tumor in cancers, ultimately resulting in neovascularization.

So basically, it can be said that change in the body’s metabolic activity also affects the rate of angiogenesis. But it should be noted that it is a reversible process which means when metabolic activity of the body reverck 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 edema, macular degeneration, glaucoma, haemorrhage in vitreous, diabetic retinopathy, ocular tumors like retinoblastoma, haemangioma, etc.

Angiogenesis is controlled bsignalingling system comprising positive feedback and negative feedback that 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.

4. 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.

DISCLAIMER

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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Angiogenesis Inhibitors [Internet]. National Cancer Institute. 2021 [Cited 18 November 2021]. Available:https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/angiogenesis-inhibitors-fact-sheet
2. PC. [VEGF, anti-vEGF and diseases] [Internet]. Pub Med; 2021. [Cited 18 November 2021]. Available:https://pubmed.ncbi.nlm.nih.gov/18819684/
3. Adair T, Montani J. Regulation: Metabolic Factors [Internet]. Ncbi.nlm.nih.gov; 2021. [Cited 18 November 2021]. Available:https://www.ncbi.nlm.nih.gov/books/NBK53243/
4. CSM, AB B, SŞ, MM, CM, MI et al. Vascular endothelial growth factor (VEGF) - key factor in normal and pathological angiogenesis [Internet]. Pub Med; 2021. [Cited 18 November 2021]. Available:https://pubmed.ncbi.nlm.nih.gov/30173249/
5. Stefan Cornel H. Anti-vascular endothelial growth factor indications in ocular disease [Internet]. PubMed Central (PMC); 2021.

[Cited 18 November 2021].
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5712945/

6. Gopang Z, Bhutto SA, Abbasi SA, Abbasi FA, Nagdev V. Efficacy of Treatment of Diabetic Macular Edema through Frequency-Doubled ND: YAG Laser (532NM) Green Laser. Journal of Pharmaceutical Research International. 2021:129-34.
7. Anti-VEGF Treatments [Internet]. American Academy of Ophthalmology; 2021
[Cited 18 November 2021].
Available:https://www.aao.org/eye-health/drugs/anti-vegf-treatments
8. Yeola, Meenakshi Eknath, and Aditya Prabhalkarrao Borgaonkar. Passage of Gangrenous Small Bowel Per Rectum Following Superior Mesenteric Vessel Thrombosis. Journal of Clinical and Diagnostic Research. 2019;13(12).
Available:https://doi.org/10.7860/JCDR/2019/42828.13381.
9. Shinde R, Dighe S, Shinde S. A rare case of triple vessel disease of abdomen. Medical Science. 2021;25(107):101–5.
10. Dongre, Parag Yashwant, Aruna Chandak V. Comparison of 0.75 % Ropivacaine with 0.5 % Bupivacaine in Peribulbar Block in Ophthalmic Surgeries. Journal of Evolution of Medical and Dental Sciences-JEMDS. 2020;9(36): 2641–44.
Available:https://doi.org/10.14260/jemds/2020/574.
11. Sune, Mona P, Pradeep Sune, and Vishal Kalode. Review of SARS-CoV-2 and Conjunctivitis: Ophthalmologists Be Safe. Journal of Clinical and Diagnostic Research. 2020;14(10).
Avaialble:https://doi.org/10.7860/JCDR/2020/44972.14116.
12. Pareek, Aditi, Aditya Khandekar, Sourya Acharya, Pravin Tidake, and Samarth Shukla. Correlation between Nephropathy and Ophthalmic Complications in Cases of Sickle Cell Anemia: An Entangled Association. Indian Journal of Medical Specialities. 2019;10(2): 72–75.
Avaialble:https://doi.org/10.4103/INJMS.INJMS_4_19.
13. Daigavane SV, Abhishek GU. Total Ophthalmoplegia as a Presenting Feature in Nasopharyngeal Carcinoma - A Case Report. Journal of Evolution of Medical and Dental Sciences-JEMDS. 2021;10(4): 236–9.
14. Jaiswal S, Bajpayee N, Abhishek GU. A Rare Case of Internal Carotid Artery Aneurysm Presenting as Total Ophthalmoplegia. Journal of Evolution of Medical and Dental Sciences-JEMDS. 2021;10(7):454–7.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/80329