

**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 its 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 its action and application of this therapy in ophthalmology is also becoming wider and wider. The implications of anti-VEGF drugs 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).

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

53

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

61

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

66

### 67 **OBJECTIVES**

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

69

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

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

73

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

75

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

77

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

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80

### 81 **MECHANISM OF ANGIOGENESIS**

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

85

86 *But what these factors are really?*

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

90

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

96

97 For the formation of embryonic vascular system, a signalling system is required and is also  
98 dependent on VEGF.

99 Angiogenesis occurring in pathological conditions is also correlated with the stimulation of  
100 this signalling system.

101 Be it either any physiological condition or a pathological condition, ischaemia or hypoxia can  
102 directly or indirectly stimulate the “proangiogenic factors” and its receptors. There are many  
103 factors that are involved in this process and are as following-

104  
105 a. VEGF A and its receptors – VEGFR1; VEGFR2

106 b. Placental growth factor

107  
108 c. Transforming growth factor (beta)

109  
110 d. fibroblast growth factor

111  
112 2. Hypoxia inducible factor-1 (abbreviated as HIF-1) regulates the VEGF-A via VEGFR1  
113 which itself is oxygen dependent for being regulated.

114  
115  
116 Proangiogenic factors are not the only ones that can be regulated by hypoxia since there are  
117 anti-angiogenic factors that are stimulated by a hypoxic environment such as:  
118 a. thrombospondin-1

119  
120 b. endostatin

121  
122  
123 It is important to note that, angiogenesis due to hypoxic environment is not an irreversible  
124 process as it can reverse on removal of the hypoxic stimulus and when the normal conditions  
125 are restored and the homeostasis is again maintained.

126  
127 However, we’ll talk about what happens after angiogenesis is induced to due to oxygen-less  
128 environment. Now, that angiogenesis has taken place the vascularity is bound to increase as  
129 the oxygen demand in the affected area rises up. So, to counter that oxygen demand  
130 neovascularisation occurs and increase in capillary surface, decreased diffusion of gases in  
131 the blood and adequate supply of blood in the body.

132  
133 Now, when a regulation cycle has positive feedback, negative feedback also always exists in  
134 the nature. So, when the oxygen demands of the body have been met, both pro and anti –  
135 angiogenic factors return back to an optimum level and these signals ultimately stop the  
136 furthermore development of blood vessels.

137  
138 Basically, this mechanism is directly related to the increased or decreased metabolic activity  
139 of the body.

140  
141 A nucleoside, named, adenosine also plays a role in this. Hypoxic tissues produce adenosine  
142 from ATP which further returns the balance between oxygen demand and oxygen supply (3).

143  
144 It should be noted that only VEGF-A is involved in angiogenesis. Action of VEGF-B is  
145 almost nil in this.

146

147

148 **ANTI-VEGF DRUGS**

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

152 Some of the drugs that we know of are-

- 153➤ Bevacizumab
- 154➤ Ranibizumab
- 155➤ Aflibercept
- 156➤ Pegaptanib
- 157➤ Lapatinib
- 158➤ Sunitinib

159

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

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

164

165 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.

166

167

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

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

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

174

175

176 **INDICATIONS OF ANTI-VEGF DRUGS**

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

178

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

183

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

**Comment [SB1]:** The drug is approved in EU also and this should be mentioned

**Comment [SB2]:** I think it is utterly inappropriate support the off label use of a drug.

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

188

### 189 **MACULAR DEGENERATION**

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

194

195 Studies have shown that patients on anti-VEGF therapy showed improvement in visual acuity  
196 by 15 or more letters. It may also be found in a follow up one year later that vision has  
197 improved to around 20/200 or better (5-8).

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

Comment [SB3]:

200 Monthly treatments until the drying of macula and slowly increasing time between  
201 applications can provide stable visual acuity to a patient.

202 In some patients, adverse effects are seen like inflammation in the eye or raised intraocular  
203 pressure being the most important. Others which may occur in small percentage includes  
204 vitreous haemorrhage, retinal detachment, myocardial infarction (systemic effect) etc.

205

### 206 **DIABETIC RETINOPATHY**

207 It is a very common and seriously **life-threatening** complication seen in the patients of  
208 diabetes. For so many years, it was being treated by a procedure called laser photocoagulation  
209 but as its name suggests using a laser can be a quite destructive process and may damage the  
210 retina further. Earlier steroids injections were also given intraocularly.

Comment [SB4]: DR is not a Life-threatening disease, yet it has a major impact on the QoL of the patients and this should be mentioned in bibliography

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211 After conduction of so many trials, it came to light that anti-VEGF drugs are preservative in  
212 nature as compared to the use of laser and vision was also improved after its use. **Patients**  
213 **who were administered anti-VEGF drug showed ~47% improvement in vision as compared**  
214 **to laser therapy which showed only ~19% improvement thus proving that anti-VEGF drugs**  
215 **are almost two times more efficient than laser therapy.**

Comment [SB5]: Pls provide reference

216 In this also, the preferred route is intravitreal.

217 Sometimes, both laser therapy and anti-VEGF therapies are combined and have resulted in a  
218 good outcome.

219

### 220 **NEOVASCULAR GLAUCOMA**

221 It is a secondary type of glaucoma and also a common indication of anti-VEGF drug use.

222 Anti-glaucoma drugs are available but use of anti-VEGF drugs has also shown very  
223 promising results by reducing the neovascular vessels and bringing down the intraocular  
224 pressure within ~48 hours of administration of intravitreal injection (mostly **bevacizumab**).

Comment [SB6]: PLS PROVIDE REFERENCE

225 Earlier photocoagulation was also done as a part of treatment but now, combined treatment  
226 including photocoagulation and anti-VEGF drugs have shown better outcomes as compared  
227 photocoagulation alone.

228

### 229 **OCULAR TUMOURS**

230 It can be a retinoblastoma, retinal artery hemangioblastoma or some other tumour.

231 In all these cases, combination of anti-VEGF drugs along with chemotherapy and other  
232 available cancer treatments have shown good results in **improving vision of the patient.**

Comment [SB7]: Pls provide reference

233

### 234 **CONTRAINDICATIONS OF ANTI-VEGF DRUGS**

235 These drugs are highly contraindicated in the following-

- 236➤ If there is fibrovascular proliferation which may threaten the macula  
237➤ A patient with uncontrolled hypertension  
238➤ If the patient has known hypersensitivity to drugs  
239➤ If the patient has any type of active inflammation in the eye or around the eye.  
240➤ Patient with a cardiovascular disease.  
241➤ These drugs are also contraindicated in pregnant women and women who are lactating  
242➤ Contraindicated in children in pre-adolescent age.<sup>8-13</sup>

243  
244 As it can be very harmful for patients, who fall under the above-mentioned categories, to take  
245 anti-VEGF drugs so the doctor should be extra careful while taking history thus, avoiding the  
246 occurrence of any mishappenings.

**Comment [SB8]:** ADVERSE EVENTS OR  
ADVERSE DRUG REACTIONS ARE MORE  
APPROPRIARE

### 247 248 **COMPLICATIONS/ADVERSE EFFECTS OF ANTI-VEGF THERAPY**

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

252  
253  
254 These may include-

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

266  
267 Patients suffering from diabetes may have some worrisome adverse effects such as-  
268 Delayed healing of the wound, hypertension, proteinuria, problem in the development of a  
269 collateral vessel etc.

**Comment [SB9]:** PLS PROVIDE  
REFERENCE

### 270 271 **MATERIALS AND METHODS**

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

**Comment [SB10]:** The section should  
be placed after the AIM of the paper. More  
details should be given about filters used

### 278 279 280 281 **Discussion**

282 angiogenesis is an inevitable phenomenon occurring in both healthy and pathological  
283 scenarios resulting in newly formed blood vessels.

284 In normal conditions, an equilibrium is maintained between pro-angiogenic factors and anti-  
285 angiogenic factors which are responsible for the regulation of angiogenesis.

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

287

288 The list of conditions in which angiogenesis occurs is never ending but they broadly be  
289 divided into – physiological angiogenesis and pathological angiogenesis. Physiological  
290 angiogenesis usually includes when a person is doing strenuous physical exercise, low  
291 oxygen availability and high oxygen demand (hypoxic environment) leads to the stimulation  
292 of angiogenesis.

293 Similarly in cancers, there is increased demand for oxygen and other essential nutrients for  
294 the growing tumour, ultimately resulting in neovascularisation.

295 So basically, it can be said that change in the metabolic activity of the body also affects the  
296 rate of angiogenesis. But it should be noted that is a reversible process which means when  
297 metabolic activity of the body reverts back to normal, angiogenesis also does the same.

298 Other pathological conditions (limited to ophthalmology) in which this can also be witnessed  
299 are, such as - retinopathies, macular oedema, macular degeneration, glaucoma, haemorrhage  
300 in vitreous, diabetic retinopathy, ocular tumours like retinoblastoma, haemangioma etc.

301

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

309 Above we saw that, adenosine also plays a role in this.

310

311 As we know, anti-VEGF therapy includes various drugs but there are only 3 drugs are that  
312 are used most widely, these are ranibizumab, bevacizumab and aflibercept.

313 These drugs act by blocking the action of VEGF by restraining it from binding with its  
314 receptor (VEGFR). This prevents further occurrence of angiogenesis. Whenever a person  
315 stops taking drugs, angiogenesis continues again.

316

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

319

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

321

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

326

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

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336 **Conclusion:**

337

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

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**COMPETING INTERESTS DISCLAIMER:**

345

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

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UNDER PEER REVIEW