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Michaelson 1940:

“Under condition of Hypoxia a diffusible factor
[Factor X] is released by ischemic tissue [retina] that
leads to neovascularization of retina and anterior
segment”
In 1956 George Wise wrote, “Pure retinal neovascularization is directly related to a tissue state of relative retinal anoxia. Under such circumstances, an unknown factor x develops in this tissue and stimulates new vessel formation, primarily from the capillaries and veins.”

In early nineties: hypoxic retina produces vascular endothelial growth factor (VEGF), suggesting a role for VEGF in ocular neovascularization.

Vascular endothelial growth factor (VEGF) are important signaling proteins involved in both vasculogenesis and angiogenesis.

VEGF's normal function is to create new blood vessels during embryonic development, after injury, muscle following exercise, and new vessels (collateral circulation) to bypass blocked vessels.
- Cells deficient in oxygen, produces **HIF**, hypoxia-inducible factor, a transcription factor.
- HIF stimulates the release of VEGF, among other functions. Circulating VEGF then binds to VEGF Receptors on endothelial cells, triggering a Tyrosine Kinase Pathway leading to angiogenesis.

- There are several members of the VEGF family.
- The most important is **VEGF-A**. Other members are Placenta growth factor (PGF), **VEGF-B**, VEGF-C and VEGF-D.
- VEGF-A is a **vasodilator** and increases **microvascular permeability** and was originally referred to as **vascular permeability factor**.
- It also stimulate monocyte/macrophage migration and stimulate endothelial cell mitogenesis and cell migration.
- Also regulation of blood coagulation and vascular tone through the production of **nitric oxide** and **prostacyclin**.
When VEGF is over-expressed, it can contribute to diseases:
- Cancers that can express VEGF are able to grow and metastasize.
- Over-expression of VEGF can cause vascular disease in the retina and other parts of the body.
- Drugs such as bevacizumab and Ranibizumab can inhibit VEGF and control or slow those diseases.
The first treatment developed using a VEGF-neutralizing strategy was bevacizumab (*Avastin*), a humanized anti-VEGF antibody designed to block all VEGF isoforms.

In 1997, Genentech initiated phase 1 trials of bevacizumab **for the treatment of cancer**.

Concomitant with that, VEGF was found to play a pivotal role in neovascular age-related macular degeneration (NVAMD).

One of the first anti-VEGF therapies for NVAMD was pegaptanib (*Macugen*), an RNA aptamer that binds and neutralizes VEGF165.
Now, there are 4 major anti-VEGF agents used in treating ocular problems:

- Pegaptanib sodium (Macugen).
- Ranibizumab (Lucentis).
- Bevacizumab (Avastin).
- VEGF Trap-Eye (VTE); aflibercept or Eylea.

Macugen is a single strand of nucleic acid, thus non immunogenic in nature, that specifically binds to the 165 isoform of VEGF.

It does not affect vasculogenesis.

It is administered in a 0.3 mg dose once every 6 weeks by intravitreal injection.
Safety profile of pegaptanib

- Pegaptanib was well tolerated.
- Adverse events were mainly ocular in nature, mild, transient and injection-related.
- Serious adverse events were rare. No evidence of systemic or circulatory complications attributed to vascular endothelial growth factor.

### Available Anti-VEGF Therapies

<table>
<thead>
<tr>
<th>MOA/class</th>
<th>Molecular weight</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab Anti-VEGF-A (all isoforms) antibody fragment$^a$</td>
<td>43 kDa$^b$</td>
<td><img src="image1" alt="Structure" /></td>
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<tr>
<td>Afiblercept Anti-VEGF-A (all isoforms)/PIGF/VEGF-B recombinant fusion protein$^c$</td>
<td>97–115 kDa$^d$</td>
<td><img src="image2" alt="Structure" /></td>
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<tr>
<td>Bevacizumab Anti-VEGF-A (all isoforms) full-length antibody$^e$</td>
<td>149 kDa$^f$</td>
<td><img src="image3" alt="Structure" /></td>
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MOA = Mechanism of action; PIGF = placental growth factor
Avastin is a full-length monoclonal antibody that binds all isoforms of VEGF-A.

Bevacizumab binds directly to VEGF to form a protein complex which is incapable of further binding to VEGF receptor sites effectively reducing available VEGF.

its ocular use is off-label.

Injected intravitreal in a dose of 1.25 mg in most cases

Ranibizumab (lucentis)

is antibody fragment that binds to and inhibits the biologic activity of all isoforms of VEGF-A.

FDA Cleared for use in:
- Wet ARMD
- Retinal vein occlusion
- Diabetic Macular Edema
- Dose is 0.3 mg and 0.5 mg (more commonly used)
Both Avastin and Lucentis are recommended to be injected monthly for 3 months then repeated as needed.

**RANIBIZUMAB (LUCENTIS)**
- Antibody Fragment.
- 48 kilodaltons.
- Plasma Half Life of 3 days.
- Tens of times times higher affinity for VEGF molecules.
- Costly.

**BEVACIZUMAB (AVASTIN)**
- Full Sized Antibody.
- 148 kilodaltons.
- Plasma Half Life 20 days.
- Long action & less dosage.
- Cost's less.
The Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) revealed equivalent effects on visual acuity after 1 year of monthly administration of either bevacizumab or ranibizumab in ARMD. Similarly, the two drugs were equivalent when given as needed.

Similar results were maintained at two years, with bevacizumab showing no inferiority to ranibizumab,

Statistically non-significant trend to improved visual outcomes from injections given monthly rather than as required was noted with both drugs.
Randomized trial comparing Lucentis vs Avastin in DME are on its way but final results are not out yet.

At one study comparing both suggested that the effect on BCVA was not statistically different, but ranibizumab provided more decrease in CSMT (central subfield mean thickness).

(CATT) study raised concerns that Avastin was NOT as safe at Lucentis.

But the difference was not shown to be statistically significant in (CATT II) trials, regarding serious systemic adverse effects (death, myocardial infarction, stroke) for patients receiving either bevacizumab or ranibizumab.
VEGF Trap-Eye, also known as Aflibercept, is the most recent anti-VEGF agent.

It is a 115-kDa recombinant fusion protein consisting of the VEGF binding domains of the human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin G1.

VEGF Trap-Eye competitively inhibits VEGF also placental growth factors 1 and 2.

The new drug mainly may be helpful in patients that do not completely respond to Lucentis and Avastin.

It has the potential of lasting effect longer than Lucentis and Avastin, but so far the evidence is not terribly strong and the visual acuity results are not different.
In (Wet) Age-Related Macular Degeneration (AMD)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks.

Macular Edema Following Central Retinal Vein Occlusion (CRVO)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly)
In diabetic macular edema (DME), Eylea is recommended monthly in 2 mg doses for 5 injections, followed by 2 monthly injections.

**Ocular Indications of Anti- VEGF**
**Wet - ARMD**

- The first indication for which anti VEGF was tested and approved.
- Several early studies, (study EOP1003 & EOP1004) and VISION trial proved its efficacy.
- Among the retinal changes, the quickest to resolve were intraretinal cysts, followed by subretinal fluid. Pigment epithelial detachments were slower to resolve.

**DME**

- Now the **most common** indication for intravitreal anti-VEGF
- Several studies (RESOLVE, READ, RIDE, RISE) showed Lucentis to be superior to both sham treatment and standard treatment (laser) for DME.
- Anti-VEGF plus Prompt or deferred laser treatment provided no added statistically significant benefit to anti VEGF alone.
- Prompt laser possibly worsened visual outcomes over time compared with deferred (> 24 weeks) laser treatment.

- Some suggested benefit from adding intravitreal steroid to intravitreal anti-VEGF in pseudophakic eyes with DME not having sufficient response to anti-VEGF treatment.
- A clinical trial sponsored by the DRCR network is now in phase II investigating the benefit of such regimen.
- An open label trial of combining dexamethazone implant to Lucentis in CNM suggested beneficial effect with better outcome and less number of anti VEGF injections needed.
**BRAVO**: Intravitreal anti-VEGF improved BCVA and macular thickness in macular edema due to BRVO.

A later study by the national eye institute found that after 2 years standard (laser) treatment for BRVO is doing better than anti VEGF injections.

Central retinal vein occlusions are also amenable to ranibizumab therapy.

The Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study (**CRUISE**) trial yielded similar results.
All anti-VEGF agents have shown good results with regard to the regression of neovascularization, but they were limited by their short duration.

None of the agents can substitute for the remarkable durability of PRP that qualifies it as the gold standard treatment for PDR.

Intravitreal anti-VEGF before and with PRP has benefit in the treatment of high-risk PDR.
Average time to recurrence of retinal neovascularization following anti-VEGF treatment ranges from 1 week to 3 months.

For now, the existing indications for the use of anti-VEGF agents in PDR include:

- Before vitrectomy (5-7 days) for vitreous haemorrhage, TRD.
- Anterior segment neovascularization, preferably in those with an open angle.
- DME with PDR.
- Active PDR Resistant to PRP.
The disadvantages of anti-VEGF agents in PDR are their short-term effect with reperfusion of abnormal vessels in time, TRD through fibrous contraction,

a possible mechanism is the angio-fibrotic switch of VEGF and connective tissue growth factor (CTGF) in PDR, thus promote a switch from angiogenesis to fibrosis.

Retinopathy of prematurity (ROP)

the physiopathology of ROP is based on an increase of VEGF.

The existence of a higher concentration of VEGF in the vitreous of ROP patients has been demonstrated and compared with those who do not develop the disease.

In infants with ROP, bevacizumab was used in a dose 0.625 mg/eye, one half of the normal adult dose, and most of the babies received bilateral injections.
should anti-VEGF treatment substitute current conventional diode laser treatment?

The answer is probably: No.

Indication for anti-VEGF in ROP

- cases in which laser cannot be applied due to opacification, poor midriasis, etc.
- in cases in which laser has been applied completely and vascular activity persists as a co-adjuvant treatment, provided there is no marked fibrous component to avoid retina detachment due to membrane contraction; and
- in cases with advanced zone 1 retinopathy, where anti-VEGF can be considered as a first choice or as a co-adjuvant treatment for laser.
Neovascular Glaucoma.
Corneal Vascularization
Pterygium

Intravitreal injection of Bevacizumab penetrates quickly into the ciliary body, iris and anterior chamber angle”.
“The highest concentration is seen in the anterior chamber from day 1 to 4 after an Intra-Vitreal injection and it regresses by day 14.”
Causes regression of iris and angle neovascularization within 48 hours
SUBCONJUNCTIVAL INJECTION OF Anti VEGF for corneal neovascularization

- Dosage: 2.25 mg in 0.1ml. (exact dosage ??)
- Preferred site is to inject near corneal vascularization.
- Injection site could be more than one.
- Regression seen is usually partial and may require repeat injections.
- There is a possibility that the drug might not work in old vascularized cornea.
- The effect are less pronounced for centrally located vessels. (?? intrastromal injection of Anti-VEGF)

Subconjunctival Anti-VEGF in Pterygium

- PRIMARY PTERYGIUM:
  - Subconjunctival Bevacizumab (Avastin)
    1.25mg/0.05ml causes regression of vascularity, symptoms (irritation, redness) up to 7 wks. post injection only.
RECURRENT PTRYGIUM:

- Topical Bevacizumab (Avastin) 25mg/ml QID dosing for 3 weeks, in a case of recurrent impending pterygium prevented recurrence up 6 mths follow up.

The most common side effects in clinical trials were conjunctival hemorrhage, eye pain, vitreous floaters, increased intraocular pressure, and intraocular inflammation.

- Serious adverse events related to the injection procedure occurred with an incidence rate of less than 1% and included endophthalmitis, retinal detachment, and traumatic cataracts.
FAZ enlargement: Development of macular ischaemia following IV Avastin has been reported in single case reports.

However, macular perfusion was assessed in a prospective randomized trial and No evidence of development of macular ischaemia following IV Avastin was found.

Systemic complications

Among the systemic side effects, the most common is hypertension (for at least 6 weeks after the injection), followed by other cardiovascular complications.

Although there is a theoretical risk for arterial thromboembolic events in patients receiving VEGF-inhibitors by intravitreal injection, incidence was low (< 4%) and similar to that seen in patients randomized to placebo.
The CATT study in AMD data may not be applicable in younger diabetic patients who may have significant vascular comorbidities, and younger, liable for longer period of receiving treatment.

Progressive decrease in therapeutic response after repetitive administration of a pharmacologically active substance.

This is due to desensitization of the target tissue to the drug itself.
After the first treatment of intravitreal bevacizumab for AMD, the **median time** taken to develop tachyphylaxis was **100 weeks** (range: 31-128 weeks).

The **median number** of intravitreal bevacizumab treatments to the development of tachyphylaxis was **eight** treatments.

In some cases it occurred in **as few as five injections**.

One way to reduce the incidence of tachyphylaxis may be the **concomitant use of an intravitreal steroid**

Another option to reduce the frequency of anti-VEGF injections and tachyphylaxis might be the **use of radiation**
Active blepharitis or external ocular surface infection. These conditions should be treated appropriately first.

History of significant acute inflammation related to the agent injected.

Recent history of adverse thromboembolic event such as stroke.

Many patients take anti-platelet or anti-coagulant agents. It is not necessary to stop these before injection.

Thank you