

INCREASING USE OF Anti VEGF IN OCULAR CONDITIONS – INDICATIONS, TECHNIQUE & LIMITATIONS

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HISTORY OF VEGF

Michaelson 1940:

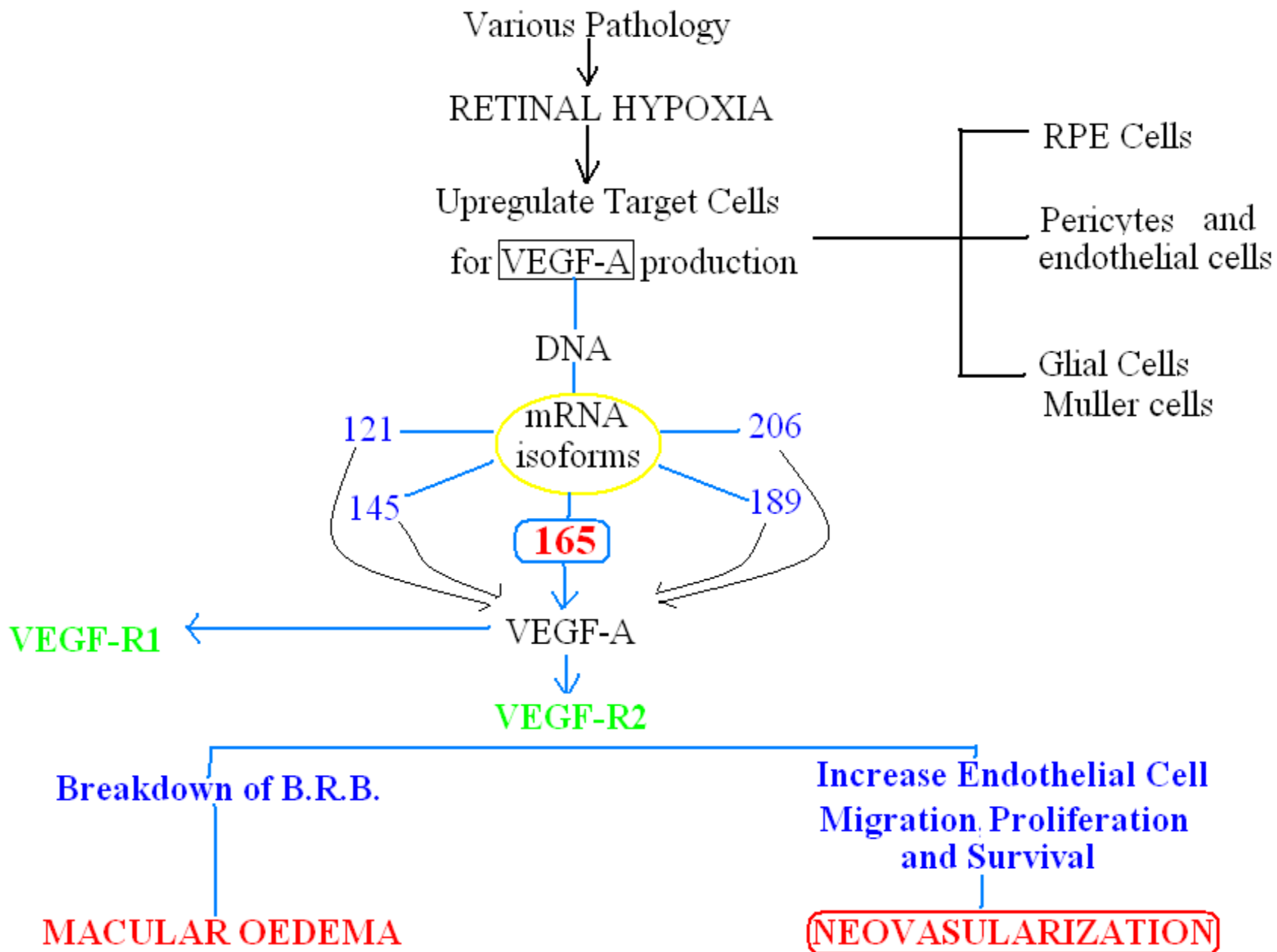
“Under condition of Hypoxia a diffusible factor [Factor X] is released by ischemic tissue [**retina**] that leads to neovascularization of retina and anterior segment”

Napoleone Ferrare and Colleagues: 1989

“A molecule in conditioned media from bovine pituitary follicular cells promotes proliferation of Endothelial cells”

This molecule went on to be known as VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

1992: It was hypothesized that the Michaelson's Factor X could be VEGF.



HYPOXIA



VEGF Isoforms



VEGF A Proteins



← Anti VEGF

VEGF receptors



Neovascularization



Retina



Anterior Segment

Anti VEGF's

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graph TD; A[Anti VEGF's] --> B[Pegaptanib]; A --> C[Ranibizumab]; A --> D[Bevacizumab]; B --> E[MACUGEN]; C --> F[LUCENTIS]; D --> G[AVASTIN]
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Pegaptanib

Ranibizumab

Bevacizumab

MACUGEN

LUCENTIS

AVASTIN

PEGAPTANIB (MACUGEN)

First Anti Angiogenic Agent

28 Base RNA Aptamer

Selectively binds
extra cellular VEGF 165

NON-IMMUNOGENIC
NATURE

DOES NOT EFFECT NORMAL
VASCUALR GROWTH

BEVACIZUMAB (AVASTIN)

- Humanized mono-clonal antibody.
- Active Against all the isoforms of VEGF's.
- FDA approved drug for treatment of metastatic colorectal cancer.

RANIBIZUMAB (LUCENTIS)

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graph TD; A[RANIBIZUMAB (LUCENTIS)] --> B[NON BINDING FRAGMENT]; A --> C[Fab FRAGMENT]; B --> D[Makes it Humanized]; D --> E[Therefore Less antigenic]; C --> F[Mouse Derived]; F --> G[Active against all Isoforms of VEGF]; G --> H[High affinity binding site];
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NON BINDING FRAGMENT

Makes it Humanized

Therefore Less antigenic

Fab FRAGMENT

Mouse Derived

Active against all
Isoforms of VEGF

High affinity binding
site

BEVACIZUMAB

(AVASTIN)

- Full Sized Antibody.
- 148 kilodaltons.
- Half Life 20 days.
- Clearance is slow.
- Long action & less dosage.
- Cost's less.

RANIBIZUMAB

(LUCENTIS)

- Antibody Fragment.
- 48 kilodaltons.
- Half Life of 3 days.
- Clearance 100 folds faster.
- 140 times higher affinity.
- Costly.

BENEFITS OF BEVACIZUMAB

- High efficacy.
- Longer half life up to 20 days and thus fewer injections.
- Lack of preservative.
- Higher safety dose: Normal i/v dose is 1.25mg
Retinal toxicity occurs at dosage > 3.5mg.
- Insignificant systemic absorption and effect.
- No experimentally proven toxicity.
- Lower cost.
- Wide availability.

INTRAVITREAL BEVACIZUMAB

- 4 ml vial of Bevacizumab has 100 mg of drug.
- In a tuberculin Syringe we take 0.05ml.
thus (1.25mg/0.05ml)
- With a 30 Gauge needle and this syringe.
- Drug is injected from the limbus
 - 3.8 mm in case of Pseudophakic.
 - 4.0 mm in case of a Phakic.

STEPS OF INTRAVITREAL BEVACIZUMAB (AVASTIN)

- Under topical anesthesia.
- Betadine painting over lid, 1-2 drops of Betadine instilled in the conjunctival sac, then washed with normal saline.
- Drug is taken in tuberculin syringe with 30G needle. (1.25mg/0.05ml)
- Ask the patient to look up.
- From the inferior-temporal quadrant at 4 mm from limbus (Phakic) the needle is directed towards the centre of the globe and drug is injected.
- Injection site pressed with a cotton bud.
- IOP and CRA perfusion is assessed.
- Topical Antibiotic is administered for one week. (TDS to QID)

COMPLICATION'S

- Vitreous Hemorrhage.
- Accidental injury to Lens capsule.
- Raised IOP.
- Retinal detachment.
- Central Retinal Artery Occlusion.
- Endophthalmitis.

REPORTS REGARDING ANTERIOR SEGMENT REACH OF INTRAVITREAL Anti VEGFS

- “Intravitreal injection of Bevacizumab penetrates quickly into the ciliary body, iris and anterior chamber angle”.
- “Penetration into Iris appears to be faster than that into ciliary body and anterior chamber angle.”
- “The highest concentration is seen in the anterior chamber from day 1 to 4 after an Intra-Vitreous injection and it regresses by day 14.”

European Ophthalmic Review 2009; 3(1): 36-38

ADVANTAGE OF Anti VEGF IN NVI & NVA

- Causes regression of iris and angle neovascularization within 48 hours.
- IOP lowering effect seen in some cases.
- A window period is gained during which an effective P.R.P can be done.
- Effective in reducing the chances of failure of and intra operative bleed during filtering surgery, when given 48-72 hours prior to surgery.

Co-Relation between VEGF concentration and NVI / NVA

RETINAL HYPOXIA



VEGF Conc. > 890 pg/ml of Aqueous



Iris and Angle Neovascularization



Intravitreal injection of Anti VEGF (AVASTIN)



VEGF Conc. < 550 pg/ml of Aqueous



NEOVASCULARIZATION REGRESSES

ANTERIOR SEGMENT USES OF Anti - VEGF

- Glaucoma
 - Iris and Angle Neovascularization
 - Neovascular Glaucoma
 - During Trabeculectomy for NVG
- Corneal Vascularization
- Pterygium

CAUSES OF NEOVASCULARIZATION OF IRIS & ANGLE

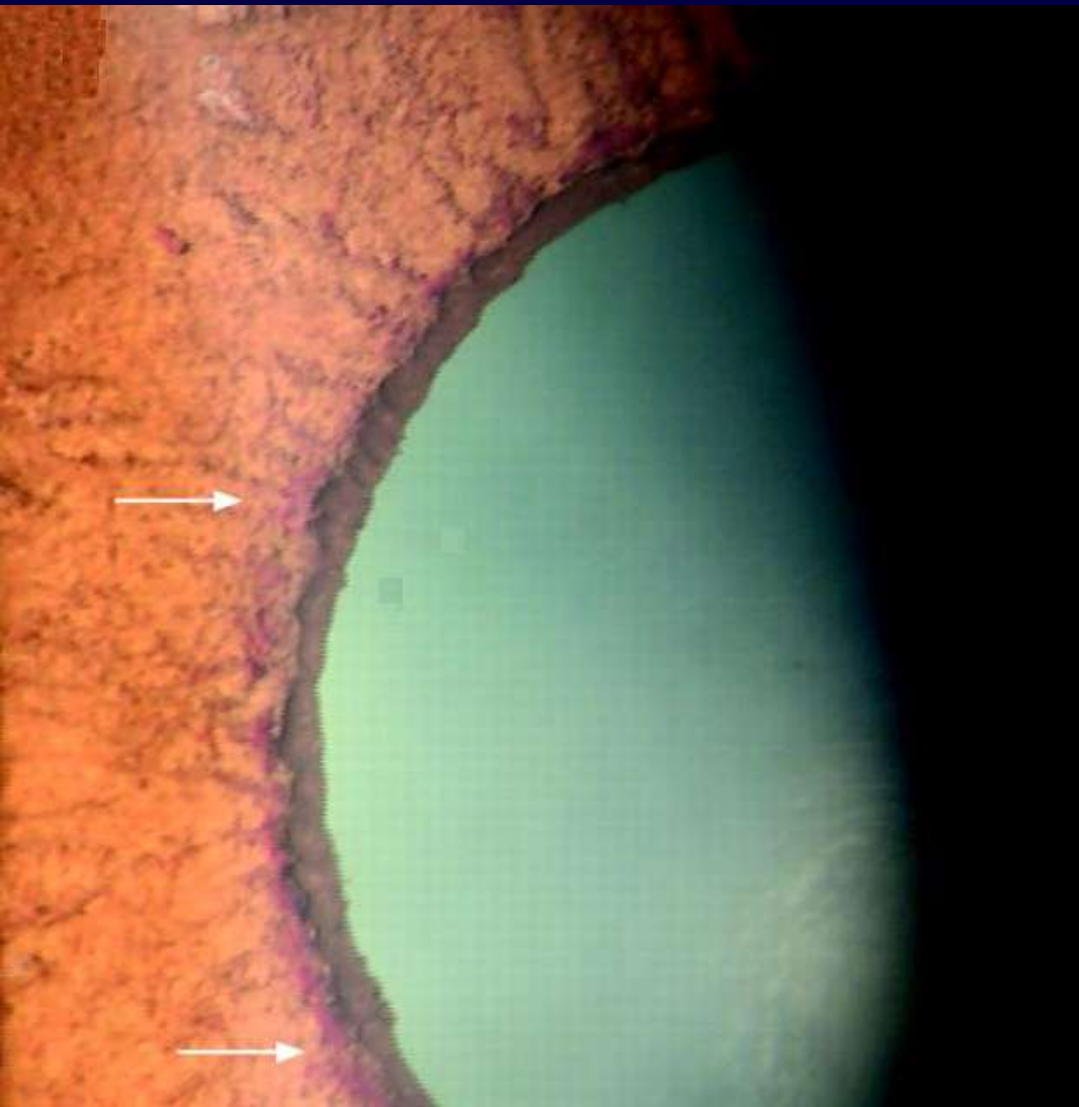
- Ocular vascular Diseases:
 - Ischemic CRVO
 - Diabetic Retinopathy
 - BRVO
 - CRAO
 - Choroidal Hemangioma
 - Sickle Cell retinopathy
- Extra Ocular Diseases:
 - Carotid artery disease/ ligation
 - Ocular Ischemia
 - Carotid Cavernous Fistula

- Other Ocular Diseases
 - Retinal Detachment
 - Eales Disease
 - Coats Disease
 - Retinopathy of prematurity
 - Persistent hyper plastic primary Vitreous.
 - Norrie's Disease
 - Sticklers Syndrome

- Ocular Inflammatory Disease
 - Chronic Uveitis
 - Sympathetic Ophthalmia
 - Endophthalmitis
 - V.K.H. Syndrome

- Post therapy
 - After Cataract Extraction in diabetic retinopathy.
 - After Vitrectomy in Diabetic retinopathy
 - Retinal Detachment Surgery
 - Post Radiation therapy
 - Laser Coreoplasty
- Ocular Neoplasm
 - Malignant Melanoma
 - Retinoblastoma

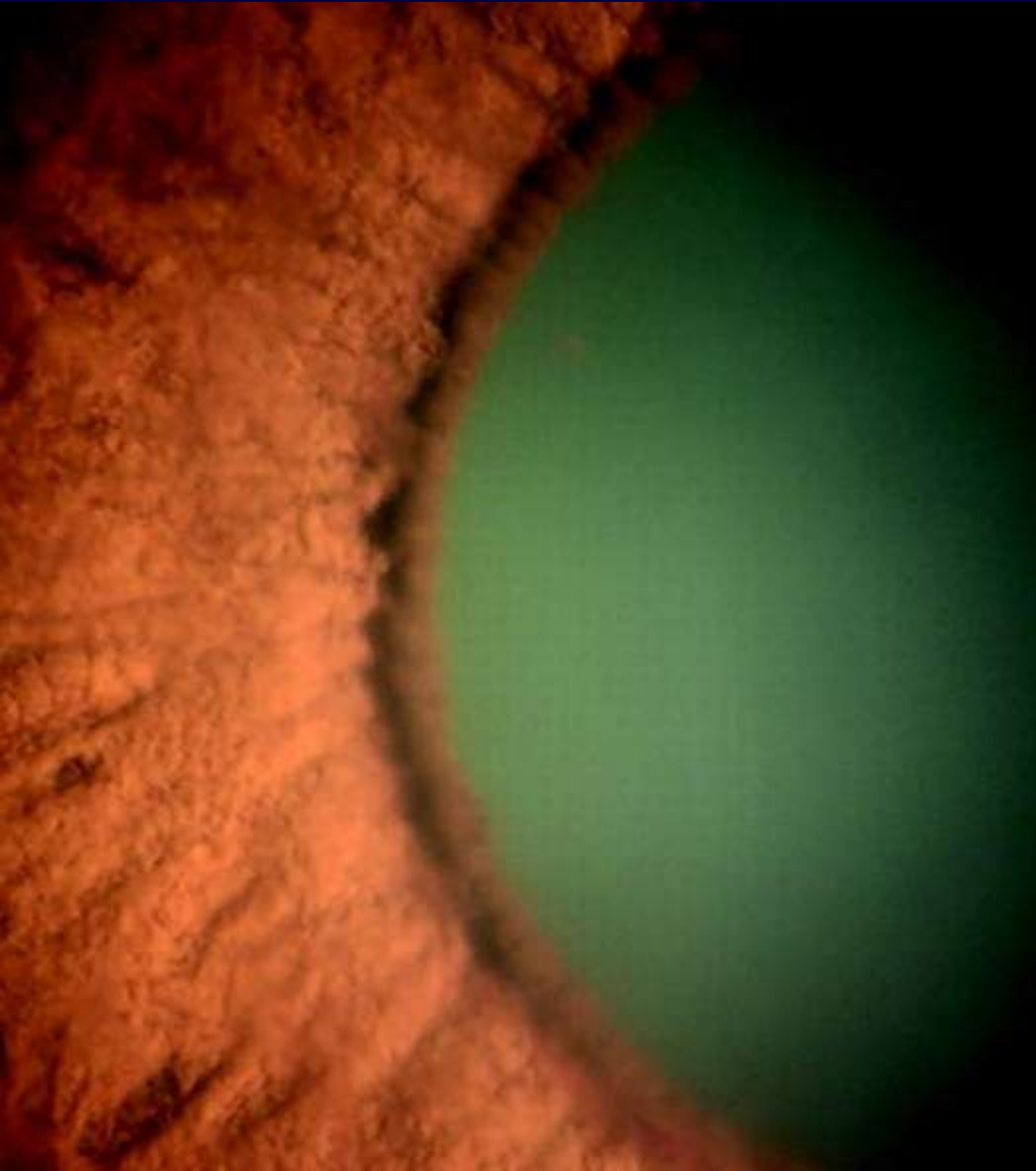
Iris Neovascularization after CRVO



Intravitreal Injection of
Avastin
(1.25mg/0.05ml)

Intracameral Injection
of Avastin
(0.25mg/0.02ml)

ONE Week after IVA injection



- Regressed NVI
- IOP = 18 mm Hg
- P.R.P was performed.

REPORTS OF ANGIOGRAPHY

Anterior Segment Angiography

Indocyanine Green

Normal Eye Glaucomatous Eye

NO LEAKS

DEMARICATION OF IRIS VESSELS

Fluorescein Angiography

Normal Eye Glaucomatous Eye

NO LEAKS

INTENSIVE LEAKS

NVI

NVA

After a Injection of IVA

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graph TD; A[After a Injection of IVA] --> B[Indocyanine Green]; A --> C[Fluorescein Angiography]; B --> D[No Change in the Vessel Demarcation]; C --> E[Marked Reduction of vascular leaks from]; E --> F[NVI]; E --> G[NVA];
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Indocyanine Green

No Change in the
Vessel Demarcation

Fluorescein Angiography

Marked Reduction of
vascular leaks from

NVI

NVA

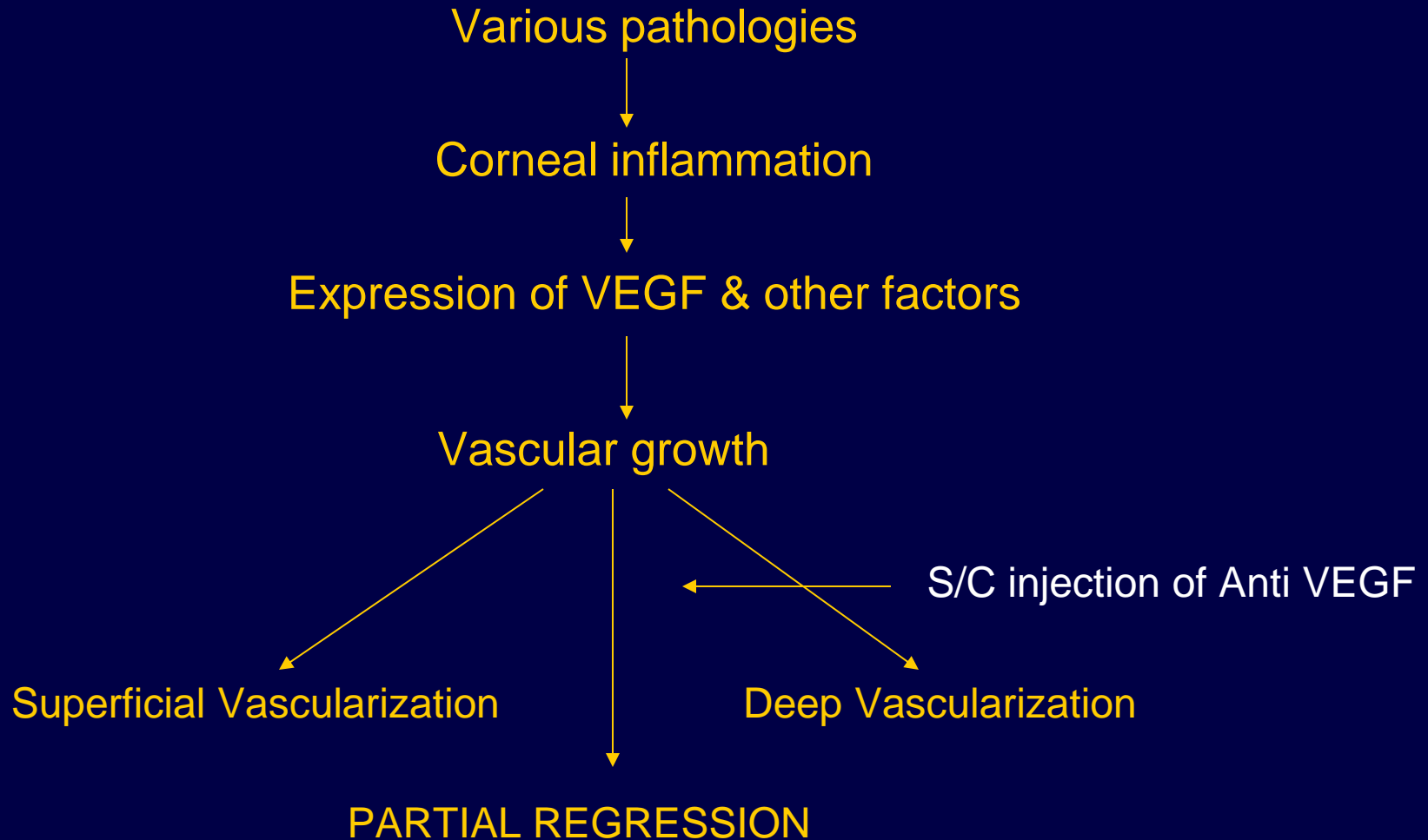
THUS CONCLUDED

- Intravitreal injection of Anti VEGF (AVASTIN) reduces the vascular permeability of the new vessels at angle and Iris.
- There is no effect on appearance of the newly formed vessels when examined by angiography.
- On Slit Lamp Examination there is a definitive regression of the neovascularization seen.

BEVACIZUMAB (AVASTIN) FOR CORNEAL VASCULARISATION

- Causes of corneal Vascularization:
 - Trauma: (physical, chemical, thermal or radiation)
 - Post infective: (viral, bacterial, fungal, protozoal)
 - Corneal dystrophies and degeneration.
 - Endothelial malfunction: (PBK, ABK, uveitis)
 - Inflammatory corneal disorders.

PROPOSED MECHANISM OF Anti VEGF ACTION



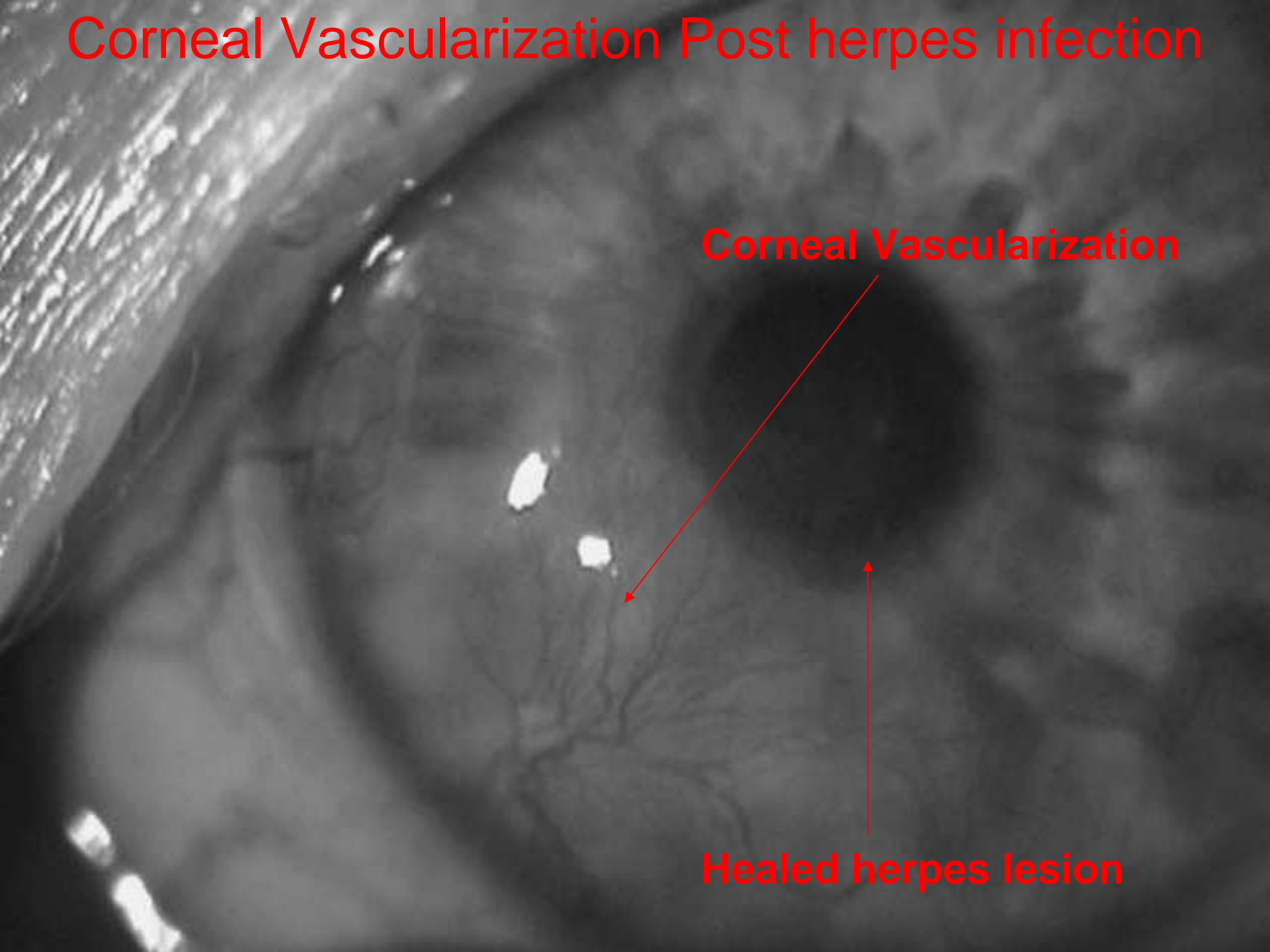
SUBCONJUNCTIVAL INJECTION OF Anti VEGF

- 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)

ADVANTAGES OF SUBCONJUNCTIVAL Anti VEGF

- Reduced vascularity of cornea.
- Better outcomes of penetrating keratoplasty.
- Visual improvement in few patients.
- Can be used in adjunct to steroid therapy or immunosuppressive drugs.

Corneal Vascularization Post herpes infection



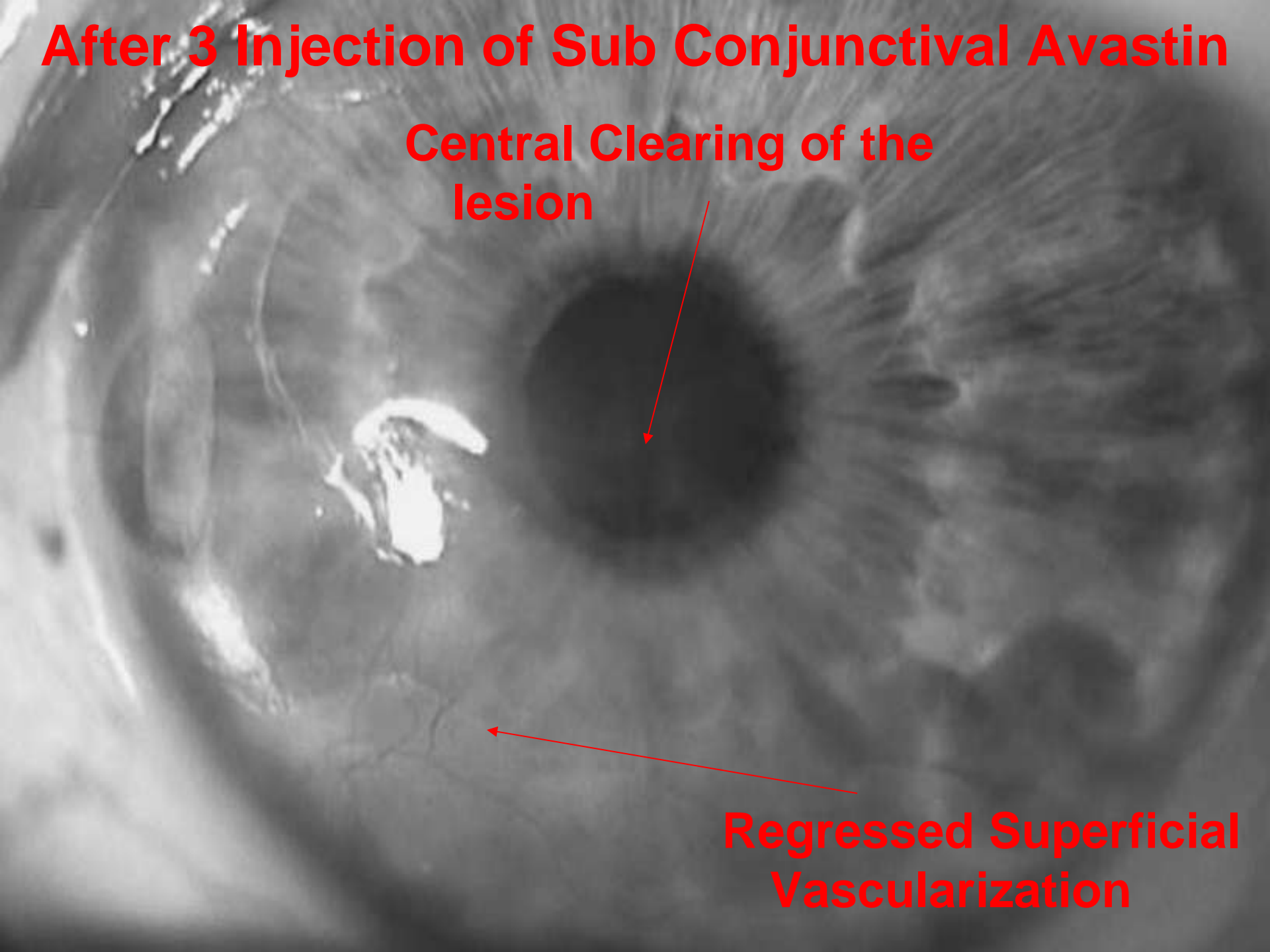
Corneal Vascularization

Healed herpes lesion

After 3 Injection of Sub Conjunctival Avastin

Central Clearing of the
lesion

Regressed Superficial
Vascularization



TOPICAL BEVACIZUMAB (AVASTIN) WITH ANTIBIOTICS

- Post operative penetrating keratoplasty cases, specially in vascularized cornea.
- Avastin is given in drop form with antibiotics drops.
- Dosage: ??? 0.01ml in 3ml antibiotic twice a week for 3 weeks.
- However topical steroids, antibiotics & lubricants are continued.

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.

Teng CC, et al. Cornea. 2009 May; 28(4):468-70

TOPICAL Anti VEGF IN PTERYGIUM

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.

Wu PC, et al. Cornea.2009 Jan;28(1):103-4

SUMMING UP

- Anti VEGF's have a definitive role in suppressing neovascularization and to some extent the severity of the disease in
 - Choroidal and Retinal neovascularization.
 - Neovascular glaucoma.
 - Corneal vascularization. (still in nascent stage)
 - Vascularization of primary & recurrent Pterygium. (still in nascent stage)
 - Ocular tumors & neoplasms.????

LIMITATIONS

- Anti VEGF cause regression of neovascularization.
- There is no effect on the basic pathology responsible for neovascularization (hypoxia).
- It's the disease that is to be cured to prevent hypoxia and its effects.
- They are a valuable ammunition in our armamentarium but alone are not curative of the condition.
- They give us time & VALUABLE breathing space during which we can plan our course of further action.

THANK YOU

FOR YOUR PATIENT HEARING