Intravitreal Injections

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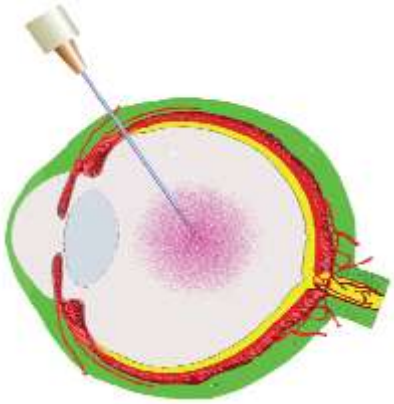
Why Intravitreal?

- To Achieve high ocular drug concentration for effective retinal diseases management with minimal systemic complications.

What to Inject?

- Antibiotics
- Corticosteroids
- Anti-VEGF
- Plasmin and microplasmin
- Combined injection



Delivery

- Direct injection through pars plana
- Sustained-release implants
- Biodegradable implants
- Recent conjugate compounds

Indications

- Ocular inflammations and infection
- Diabetic macular edema
- CRVO and BRVO
- Neovascular AMD
- Pseudophakic cystoid macular edema
- Macular edema secondary to uveitis

Antibiotics

- The most common combination
- **Vancomycin:** 1mg in 0.1ml
- **Ceftazidime:** 2.25 mg 0.1ml
- Effective against gram positive and gram negative microorganisms (Bactericidal Effect)
- New: Intravitreal **Povidone Iodine** (0.025%) in resistant cases

Steroids

- Anti inflammatory against most inflammatory mediators and cytokines
- Antiangiogenic
- Anti permeability

The rationale is that abnormal proliferation of cells as often associated with and triggered by inflammation.

Accumulation of oedema fluid is accompanied by blood-retinal barrier dysfunction that can be restored with steroid therapy.

Triamcinolone Acetonide (TAAC)

Chemical Structure

- It is a synthetic glucocorticoid (secreted by suprarenal gland).
- It is poorly soluble in water (↑ in its half life).

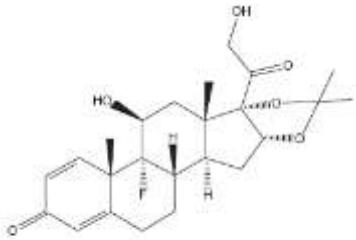


Fig. 4. Triamcinolone acetate is a glucocorticosteroid. Glucocorticosteroids have been used for their anti-inflammatory properties and as immunosuppressors for various diseases.

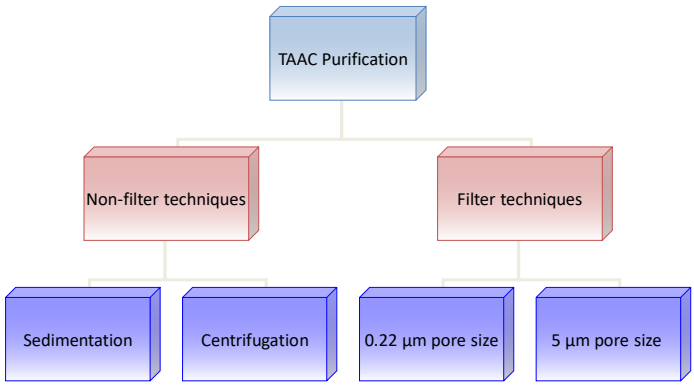
Ophthalm Clin N Am, 2005

- **Kenacort-A:** 1 ml bottle containing 40mg TAAC, 9.9 mg benzyl alcohol.
- **Kenalog-40**
- **Eperlifan** and **Amcinolone**
- **Trivaris TM** (Allergan) and **Triescence** (Alcon)

  are preservative free approved by FDA for ophthalmic use in treatment of sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory diseases non responsive to topical steroids.

Pharmacological Action

- Anti-inflammatory effect.
- Inhibition of VEGF.
- Improvement of diffusion.
- Re-establishment of blood retinal barrier through reduction of permeability.



In all, the vehicle decreased to one tenth, the difference was in TAAC conc.

For intravitreal injection

- In Egypt, the **4-mg dose** is most commonly used. I use now 2 mg.
- In Europe, Jonas and colleagues used **25-mg** injections and appeared to have similar results and rates of complications reported by 4-mg one.
- The SCORE (standard care versus corticosteroids for retinal vein occlusion), phase 3 trial of IVTA in CRVO associated macular edema is testing 3 doses, placebo, **1 mg** and 4 mg doses.

Intravitreal Implants

Ozurdex implant

- ***The dexamethasone drug delivery system (DDS)*** **[Ozurdex, Allergan, Irvine, California] is a biodegradable, sustained-release device approved by the US FDA for the treatment of macular edema associated with retinal vein occlusion and noninfectious posterior segment uveitis.**
- **A phase 2 RCT in patients with *persistent macular edema secondary to various etiologies, including DME*, showed that the dexamethasone DDS produced improvements in visual acuity, macular thickness, and fluorescein leakage that were sustained for up to 6 months.**

Retisert implant

- ***To reduce the need for repeated intravitreal injections, several extended-release corticosteroid delivery systems*** have been studied.
- ***A fluocinolone-acetonide- (FA-***) eluting intravitreal implant (Retisert, Bausch and Lomb, NY, USA) has received FDA approval for the treatment of chronic, noninfectious posterior segment uveitis
- This is ***a nonbiodegradable device that releases 0.59 µg/day*** of FA into the vitreous cavity. It must be implanted in an operating room or similar setting.

- ***Iluvien*** **is another promising sustained-release steroid, intravitreal, office-based implant that utilizes fluocinolone as opposed to dexamethasone.**
- **The advantages of this particular platform include *a smaller size* (25 ga. as opposed to 22 ga. with Ozurdex*) and a longer duration* of efficacy**

Is Steroids An Ideal agent

Effective

- **Long term VA improvement**
- **Long term CMT reduction**

In about > 50% of patients

Safe

Local and systemic side effects

Economic

Small number of injections needed

Effective (Steroids)

Triamcinolone

DRCRN 2008

visual benefit ≥10 in letter score in 25% (IVT1), 28% (IVT4) and 31% (Laser)

Gillies et al

visual benefit ≥10 in letter score in 21% (IVT) Vs 12% (control - sham)

Flucinolone:

In FAME, visual benefit ≥15 in letter score 28.7% (low dose 0.2 µg/d) and 27.8% (high dose 0.5 µg/d).

Dexamethasone

In MEAD, visual benefit ≥15 in letter score 22.2% (0.7 mg DEX implant) and 18.4% (0.35 mg DEX implant).

Safe (Steroids)

Local:

	Triamcinolone	Flucinolone	Dexamethasone
Cataract	***cataract surgery in*** **DRCRN 2008** IVT1: 23% (46% by 3 years IVT4: 51% (83% by 3 years); L: 13% (31% by 3 years) **DRCRN 2010** CPL: n=11 RPL: n=6 RDL: n=8 TPL: n=19	**FAME** ***cataract surgery in*** FA 0.2 (80%); FA 0.5 (87.2%); C: (27.3%) **Pearson et al(0.59mg)** SRFA: 55.9%; SOC: 21.7%	**MEAD** DEX 0.7mg (67.9%); DEX 0.35mg (64.1%); C: (20.4%)

	Triamcinolone	Flucinolone	Dexamethasone
IOP rise	**Lam et al** IVT: 37% Laser 5% **IOP lowering medication:** ***Gillies et al/Sutter et al*** IVT: 44% (p=0.0002 vs C); C: 3% ***Gillies et al*** IVTL: 64% (p<0.001); L: 24% **Glaucoma surgery:** **DRCRN 2008** IVT1: n=0; IVT4: n=2; L: n=0	**FAME** ***Glaucoma surgery in*** FA 0.2 (4.8%); FA 0.5 (8.1%); C: (0-0.5%) ***IOP rise at any point in*** FA 0.2 (37%); FA 0.5 (46%); C: (12%) **Pearson et al(0.59mg)** SRFA: 69.3%; SOC: 11.6%	**MEAD** ***Glaucoma surgery in*** DEX 0.7mg (0.6%); DEX 0.35mg (0.3%); C: (0%) **Haller et al** DEX 0.7mg (9.4%); DEX 0.35mg (14.5%); C: (0%)

Systemic

DRCRN 2010

No specific systemic adverse events that could be attributed to chance

Soheilian et al

No significant blood pressure increase

No thromboembolic events

Economic

For anti-VEGFs

Typically, the number of injections needed is:

8-10 in the first year

2 or 3 during the second year

1 to 2 during the third year

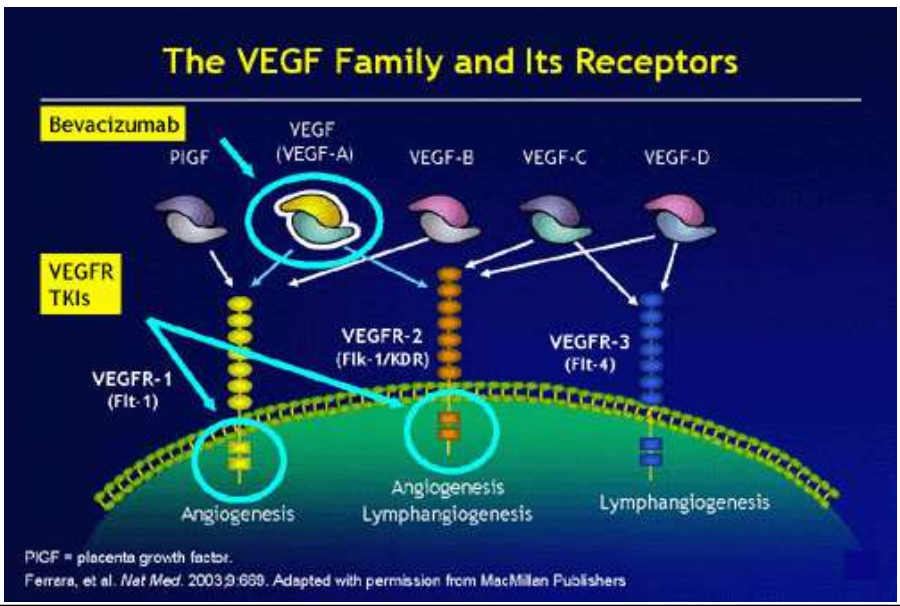
0 to 1 in the fourth and fifth years of treatment

ICO guidelines for Diabetic Eye Care 2017

For steroids

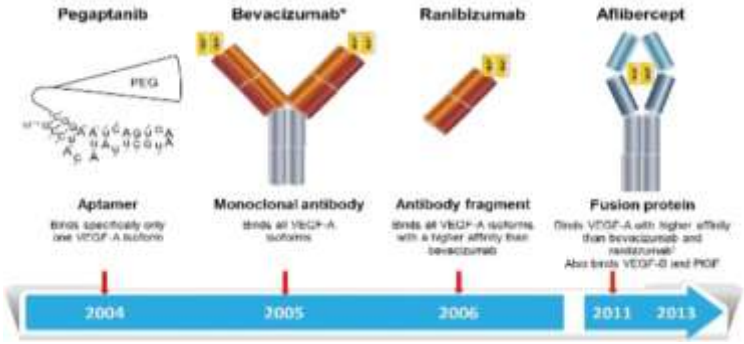
mean of 2.6 injections over 2 years for IVT4 Vs 1.8 injections in placebo control **(Gillies et al)**

Anti VEGF



Anti-VEGFs in Ophthalmology

Anti-VEGFs became treatment of choice for wAMD, DME, and RVO.



	Aflibercept	Ranibizumab	Bevacizumab	Pegaptanib
FDA approved	Yes	Yes	No (off label use)	Yes
Structure/composition	Human recombinant fusion protein	Humanized monoclonal antibody fragment	Whole humanized monoclonal antibody	Aptamer (synthetic oligonucleotide)
Size	115 kDa	48 kDa	148 kDa	28-base RNA oligonucleotide with two branched 20 kDa PEG moieties
Growth factor specificity	All isoforms of VEGF-A, VEGF-B, and PlGF	All isoforms of VEGF-A	All isoforms of VEGF-A	$VEGF-A_{165}$
Intravitreal dose for AMD (mg)	2	0.5	1.25	0.3
Intravitreal half life (days)	4.7	2.9	4.3	3.9

VEGF INHIBITORS

TABLE. Molecular Properties of Anti-VEGF Agents

Agent	Bevacizumab (Avastin, Roche/Genentech)[1]	Ranibizumab (Lucentis, Roche/Genentech)[1]	Aflibercept (Eylea, Regeneron)[1]	Brolucizumab (Novartis)[2]
Format	Full antibody (IgG1)	Monoclonal humanized antibody fragment	VEGF receptor 1/2-Fc fusion protein	Short-chain variable fragment
Molecular structure				
Molecular Weight	149 kDa	48 kDa	115 kDa	26 kDa
Clinical dose for nAMD	1.25 mg (off-label use)	0.5 mg	2 mg	6 mg
Equivalent molar dose[3]	0.8	Reference	1.7 to 2	22

1: Semeraro F, Morescalchi F, Duse S, Parmeggiani F, Gambicorti E, Costagliola C. Aflibercept in wet AMD: specific role and optimal use. Drug Des Devel Ther. 2013;7:711-722.
2. Escher D. Single-chain antibody fragments in ophthalmology. Paper presented at: 15th EURETINA Conference; September 17, 2015; Nice, France.
3. Holz F. Results from two phase II studies evaluating safety and efficacy of RTH258, a single-chain anti-VEGF antibody fragment in patients with neovascular AMD. Oral presentation at: 15th EURETINA Conference; September 19, 2015; Nice, France. Images courtesy Novartis.

Hypoxia and Oxidative stress

↓

RPE

↓

VEGF-A

↓

Angiogenesis
Chemotaxis
NO release

↓

Macular odema
Neovascular AMD
Proliferative retinopathies

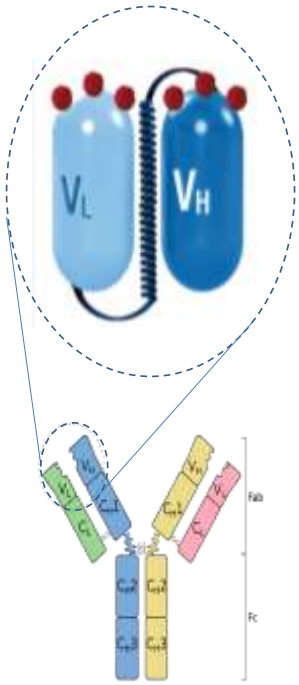
BROLUCIZUMAB (Vsiqq)

Single-chain variable antibody fragment (26kDa → higher molar dose → ↑tissue penetration & ↑duration of action)

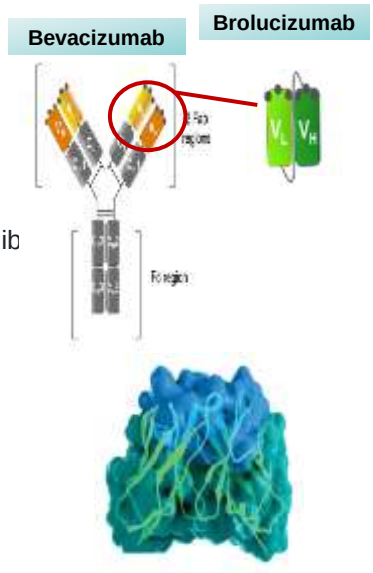
KITE & KESTREL phase 3 trials → patients needed fewer injections to achieve VA comparable to aflibercept.

6mg injection/6 weeks for five doses, followed by one injection every 8–12 weeks.

FDA granted approval June 2022 but included a warning about retinal vasculitis & retinal vascular occlusion.



Brolucizumab (Vsiqq)



Single-chain variable fragment (**scFv**) =>Inhib VEGF-A

Low Mw (26 KDa) => better affinity to receptors + longer half life

Phase 3 **HAWK** and **HARRIER** Trials Brolucizumab has a superior control of nAMD exudative features

FDA approved in 2020 (**Bevou™**)

Molecular structure

Advantages

Durable / longer half life

Better drying effect of the retina

Drawbacks

FDA Safety alert June 2020

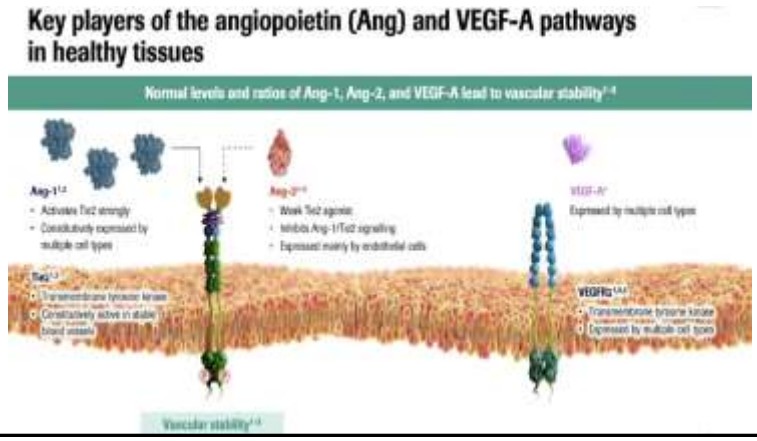
June 17, 2020

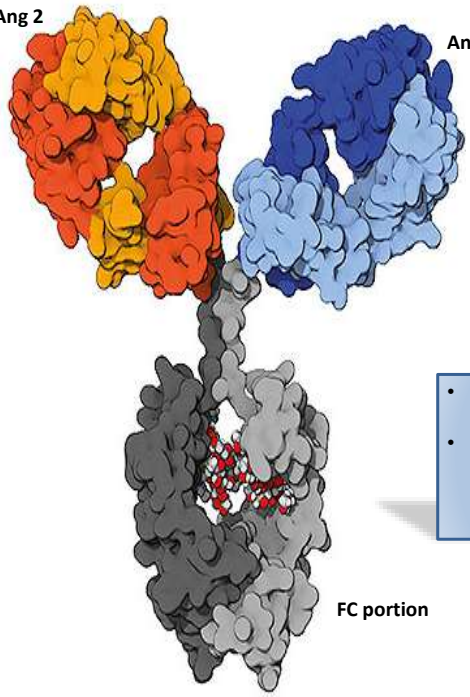
Beovu Label Change: Warnings About Possible Permanent Vision-Loss Side Effects Added In June 2020

Beovu Use Increased Risks Of Retinal Vasculitis And Retinal Vascular Occlusion, Which Can Lead To Blindness

Drugs targeting the Angiopoietin (Ang) pathway:

-There are 2 types of Angiopoietin 1 and 2.





FARICIMAB Vabysmo

Bispecific monoclonal Ab
Received FDA approval January 2022
6mg in 0.05ml of 120mg/ml solution

- **Phase 2 trials (BOULEVARD): superior to ranibizumab**
- **Phase 3 trials (RHINE & YOSEMITE): superior to aflibercept & prolonged activity allowing extended intervals up to 3 or 4 months**

Faricimab (Vabysmo)

- Bispecific antibody

- Targeting both VEGF-A and angiopoietin-2 to reduce treatment load

.

-TENYA and LUCERNE for wet AMD and YOSEMITE and RHINE for DME , BOULEVARD .
compare aflibercept and ranibizumab to faricimab.

Thank you