Intravitreal Steroids: Do We Still Need Them?

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Steroids

- Anti inflammatory
- 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.

Why Intravitreal?

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

Delivery

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

Indications

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

Triamcinolone Acetonide (TAAC)

Chemical Structure

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

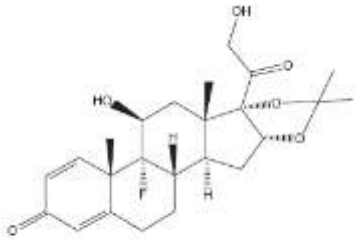


Fig. 4. Triamcinolone acetate is a glucocorticosteroid. Glucocorticosteroids have been used for their anti-inflammatory properties and as immunosuppressors for various diseases.

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.

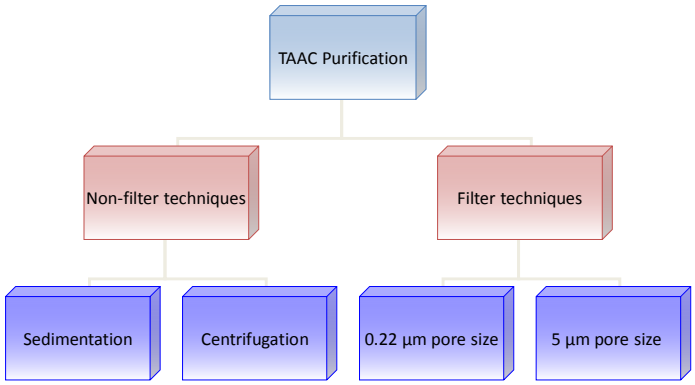
Indications of IV-TAAC in DR

- **Medical:**

  DME: (Diffuse DME, cystoid macular edema, persistent DME after laser treatment, and in conjunction with phacoemulsification in DME patients).

- **Surgical:**

  Better visualization of vitreous gel and posterior hyaloid during vitrectomy, and to decrease post operative inflammation and PVR.

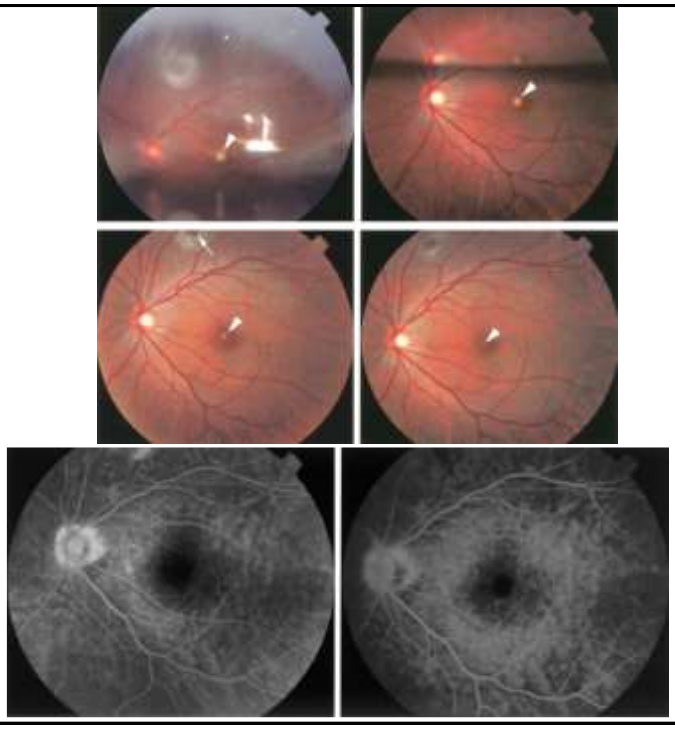


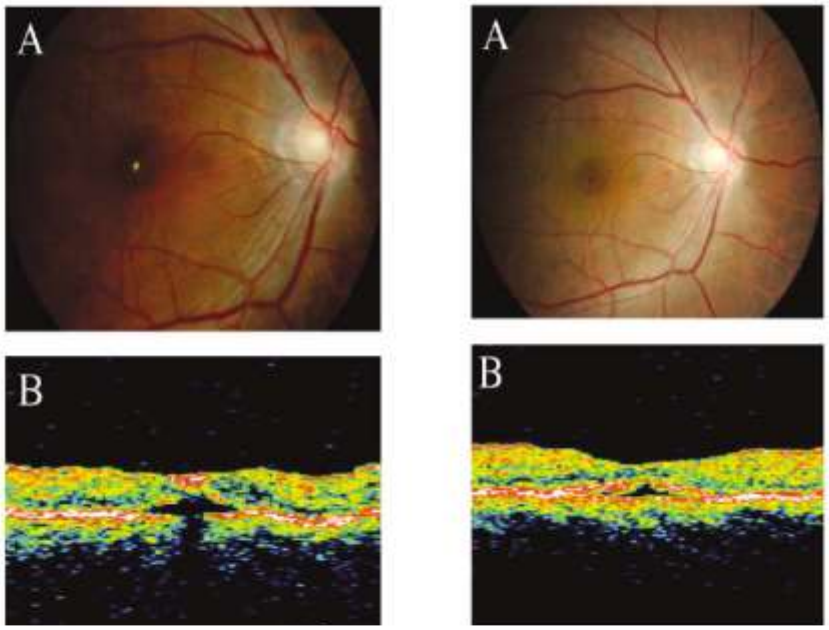
In all, the vehicle decreased to one tenth, the difference was in TAAC conc.

For intravitreal injection

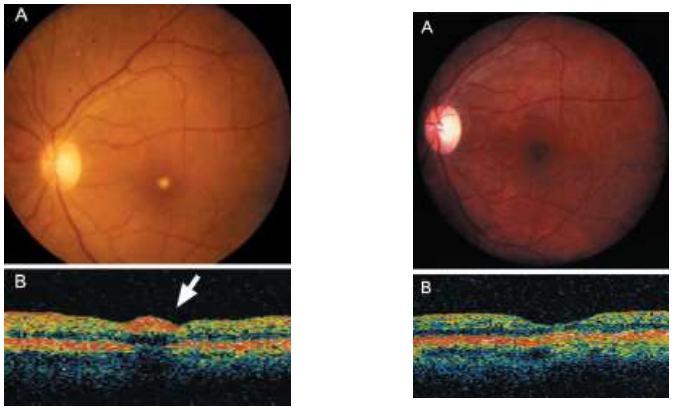
- In Egypt, the **4-mg dose** is most commonly used. I use now 2 mg.
- In Europe, Jonas and colleagues used **25-mg** injections and appeared to have similar results and rates of complications reported by 4-mg one.
- The SCORE (standard care versus corticosteroids for retinal vein occlusion), phase 3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

Toxicity





AJO, December, 2003



12 days after surgery

41 days after surgery

Retina, January 2007

Contraindications of IV TAAC

- Chronic Simple Glaucoma.
- Steroid responder patients: 1 month of treatment with topical 0.1% dexamethasone is prescribed. If there is rise in IOP > 15 mmHg after 1 month, the procedure is cancelled.

Complications of TAAC

Complications Related to Injection Procedure

- Lens perforation.
- Vitreous hemorrhage.
- Retinal detachment: (Avoid superior vitreous → TAAC weight → vitreal traction → RD?), lower vitreal injection causing settling down of TAAC and avoid weight traction).
- CRAO??

Post Injection complications

2ry Ocular hypertension, 2ry Steroid Induced OAG.

IOP	Incidence
> 21 mmHg	36.2%
> 30 mmHg	8.5%
> 35 mmHg	4.2%
> 40 mmHg	1.5%

N.B: This applies to 25mg dose

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- In most cases, the rise of IOP occurred 1 to 2 months after injection. In few, it is started as early as 1 week.
- It usually lasts for 7 to 9 months.
- Patients at risk are young age, and CRVO patients.

Interesting notes about TAAC & IOP

- Post injection rise in IOP did not vary significantly between patients with pre injection Ch S G and patients without glaucoma.
- ↑ in IOP is associated with ↑ in VA. (mechanical).
- The patients who received 2nd injections showed similar behaviour as the 1st injection as regards IOP change (no cumulative effect).

Management of refractory glaucoma following TAAC injection

- Trab with mitomycin.
- Selective Laser Trabeculoplasty (SLT)
- Vitrectomy.

Endophthalmitis

- Pseudoendophthalmitis.
- Sterile endophthalmitis.
- Infectious endophthalmitis.

Steroid induced cataract

- Intravitreal TAAC leads to clinically significant cataract with eventual cataract surgery in about 15-20% of eyes within about 1 year after injection (144 phakic eye study).

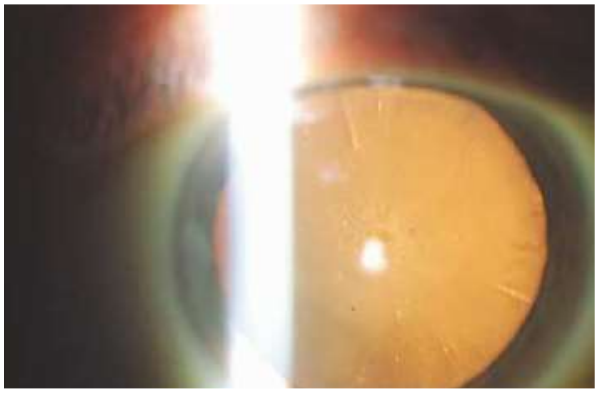
Progress in Retina and Eye Research, 2005

- Cases with 2ry IOP rise are at a higher significant risk of PSC cataract.

Ophthalmology, January 2005

Cataract 2 years after TAAC

- Incidence: 81%.
- 74% are PCO.



Eye, 2007

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.

- In an RCT, the effects of ***the device versus photocoagulation*** for DME were studied. At one year, DME was resolved by clinical examination and optical coherence tomography (OCT) in ***57% of patients with the FA implant versus 20% of patients with photocoagulation***.
- There were no statistically significant differences in final visual acuity between the two groups At 3 years, patients randomized to receive the FA implant had persistent treatment of macular edema, but 95% of phakic eyes ***developed significant cataract, and about one-third of eyes had IOP above 30 mm Hg .***

- ***The Fluocinolone Acetonide for Macular Edema (FAME) study*** comprised 2 phase 3 RCTs assessing the efficacy and safety of ***0.2 µg/day (low dose) and 0.5 µg/day (high dose***) inserts in patients with DME with persistent edema despite at least one macular laser treatment The primary study endpoint was defined as improvement in visual acuity by 15 or more letters at 2 years. At 24 months, the primary endpoint was achieved ***in 28.7% and 28.6%*** of low- and high- dose insert groups compared with 16.2% in the sham group. Elevated intraocular pressure requiring incisional surgery occurred ***in 3.7%, 7.6%,*** and 0.5% of the low-dose, high-dose, and sham groups, respectively. ***(Campochiaro P, et al 2012)***

- ***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 (2.5 to three years).**

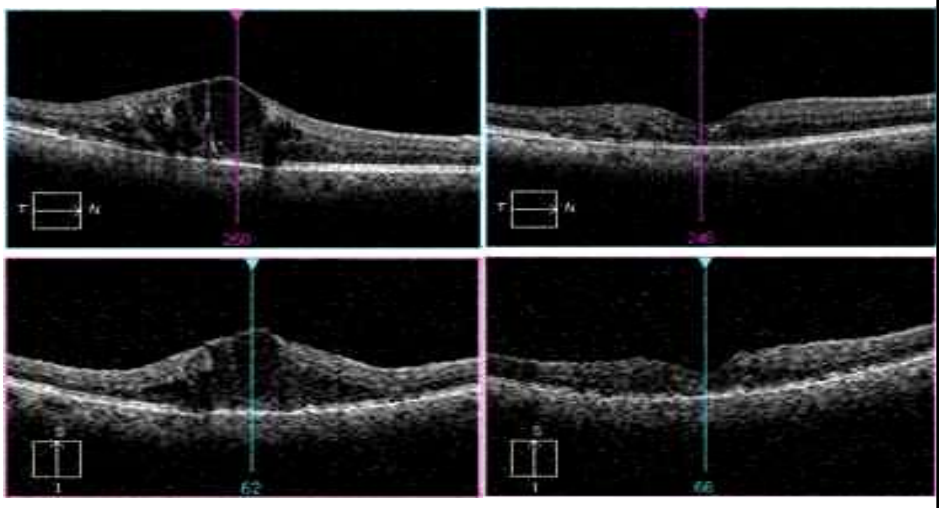
- **FAME, a prospective, randomized trial, just published its three-year data.17 The trial evaluated two different doses of steroid implant (0.2 µg /day versus 0.5 µg /day) versus sham control. At three years, the percentage of >15 letters of vision gained was 28.7 percent (0.2 µg /day) and 27.8 percent (0.5 µg /day) in the implant groups compared with 18.9 percent (p=0.018) in the sham group. Virtually all phakic patients developed cataracts, but their visual benefit after cataract removal was similar to that of patients who were pseudophakic at baseline. The incidence of incisional glaucoma surgery was found to be 4.8 percent in the low-dose group and 8.1 percent in the high-dose insert group.**

Ozurdex implant

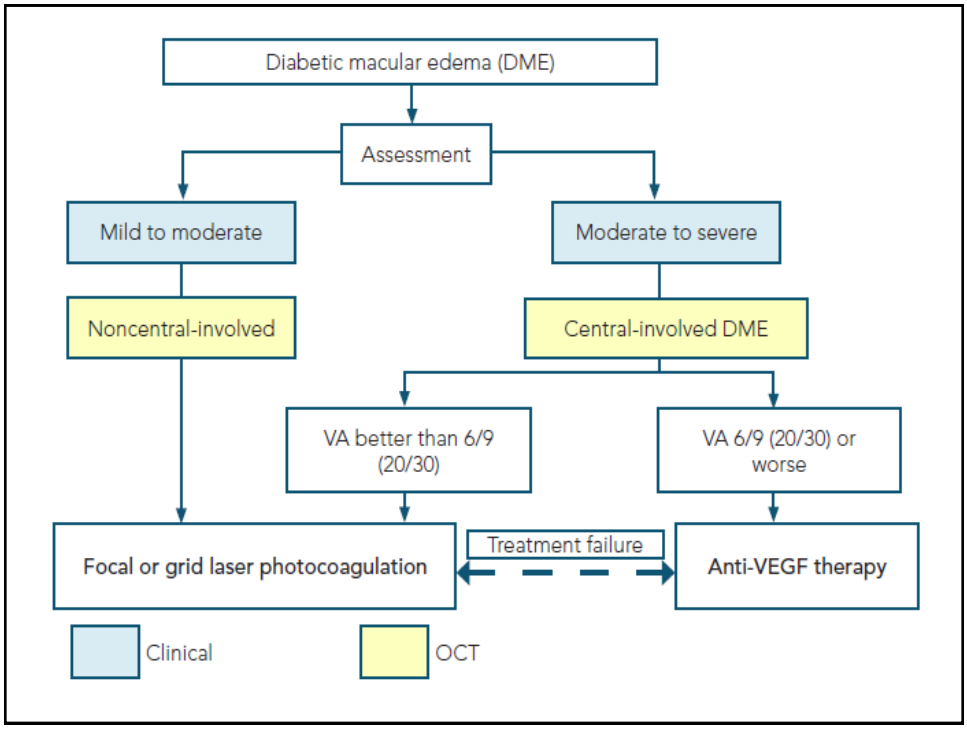
- ***The dexamethasone drug delivery system (DDS)*** **[Ozurdex, Allergan, Irvine, California] is a biodegradable, sustained-release device approved by the US FDA for the treatment of macular edema associated with retinal vein occlusion and noninfectious posterior segment uveitis.**
- **A phase 2 RCT 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.**

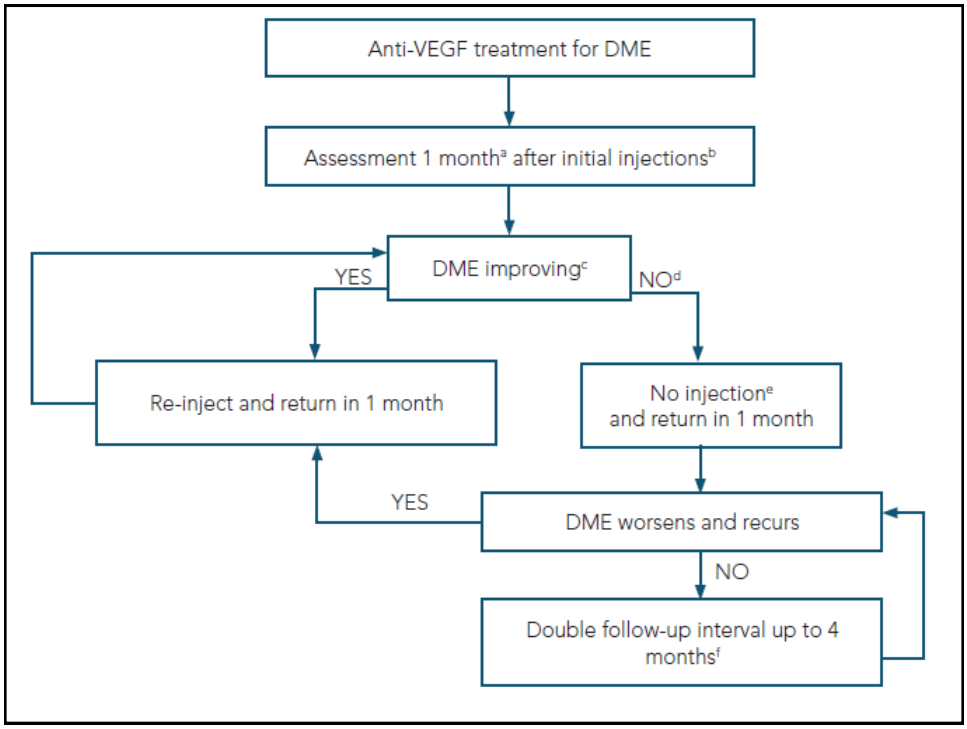
- **Patients with persistent macular edema (at least 90-day duration) were randomized to treatment *with 700 µg or 350 µg* of dexamethasone DDS or observation. At 3 months, visual acuity improved by 10 letters or more in 30% of eyes in the 700 *µ*g group, *20%* of eyes in the 350 *µ*g group, and *12%* of eyes in the observation group. A more recent study reported that the dexamethasone DDS improved visual acuity and macular edema in previously vitrectomized eyes with diffuse DME.**

(Boyer D, Faber D, Gupta S, et al. Dexamethasone Intravitreal Implant for Treatment of Diabetic Macular Edema in Vitrectomized Patients. Retina 2011;31:915-923)



Guidelines for treatment of DME


Diabetic macular edema (DME)
Assessment
Mild to moderate
Moderate to severe
Noncentral-involved
Central-involved DME
VA better than 6/9 (20/30)
VA 6/9 (20/30) or worse
Focal or grid laser photocoagulation
Treatment failure
Anti-VEGF therapy
Clinical
OCT


Anti-VEGF treatment for DME
Assessment 1 month[a] after initial injections[b]
DME improving[c]
YES
NO[d]
Re-inject and return in 1 month
No injection[e] and return in 1 month
YES
DME worsens and recurs
NO
Double follow-up interval up to 4 months[f]

What should we do in persistent retinal thickening despite of anti- VEGF therapy?

1- Shift to another anti-VEGF

Indian guidelines 2016

2- Consider steroids (triamcinolone, flucinolone or dexamathasone)

ICO guidelines 2017

3- Consider vitrectomy

Controversies

Steroids and laser therapy may affect CMT in a different manner from anti-VEGF drugs

when ***triamcinolone plus laser*** is compared with ***ranibizumab plus laser***, the latter appears to be more effective in terms of change in BCVA and proportion of patients with more than 15 letter gain, but triamcinolone plus laser is more effective at reducing CMT.

There is a weak correlation between CMT and BCVA

Ford JA, Lois N, Royle P, et al. BMJ Open 2013;3:e002269

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)**

CONCLUSION

- **Anti- VEGFs** are more effective at improving vision but high number of injections needed
- **Steroids** are more effective at reducing CMT but with high incidence of cataract and IOP rise
- **Laser** (prompt or deferred) has no visual benefit but may be more effective at reducing CMT and decreasing the number of injections needed

- **Steroids is mandatory in certain diseases**
- **The debate about their use is still going on in DME**
- **New advances in methods of administration are under research.**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Thank you