Intravitreal injections

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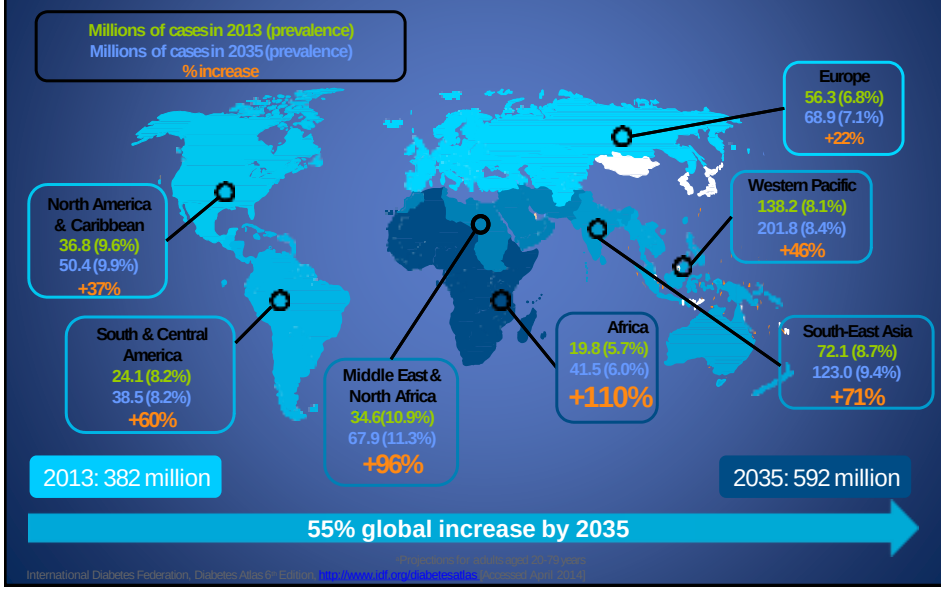
Global projections for diabetes[a]



[a]Projections for adults aged 20-79 years

International Diabetes Federation, Diabetes Atlas 6th Edition, http://www.idf.org/diabetesatlas (accessed April 2014)

VEGF

- VEGF is a short form for vascular endothelial growth factor, which is responsible for growth of blood vessels.
- VEGF is also responsible for many retinal diseases by causing new vessels growth and by increasing leakage and thus causing retinal swelling.

VEGF-A

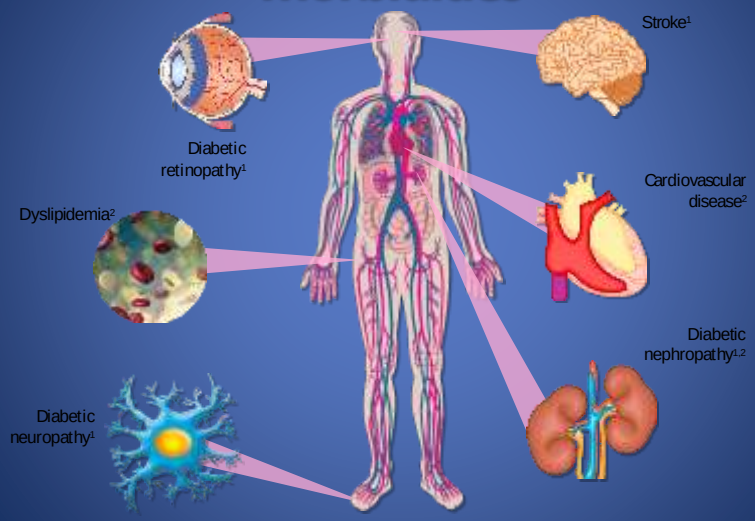
- **VEGF family is 7 types of members the most important in ophthalmology is VEGF A and the most important isoform is the VEGF165**
- **VEGF-A is a chemical signal that stimulates angiogenesis in a variety of diseases, specially in cancer.**
- **Bevacizumab was the first clinically available angiogenesis inhibitor in the US.**

Anti-VEGF

- **The anti-VEGF agents block the VEGF molecules and thus benefit the patients by decreasing the abnormal and harmful new blood vessels formation and by decreasing the leakage and swelling of the retina.**

This leads to stabilization of vision and even improvement in many cases.

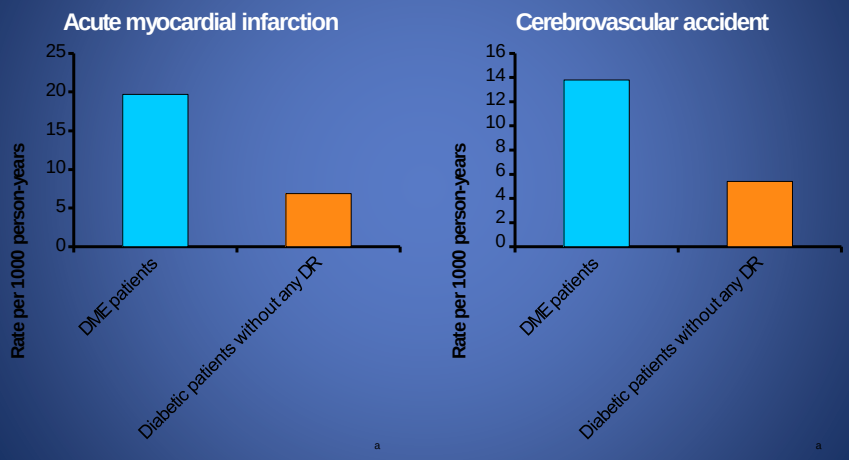
Patients with DME have systemic co-morbidities



DME, diabetic macular edema

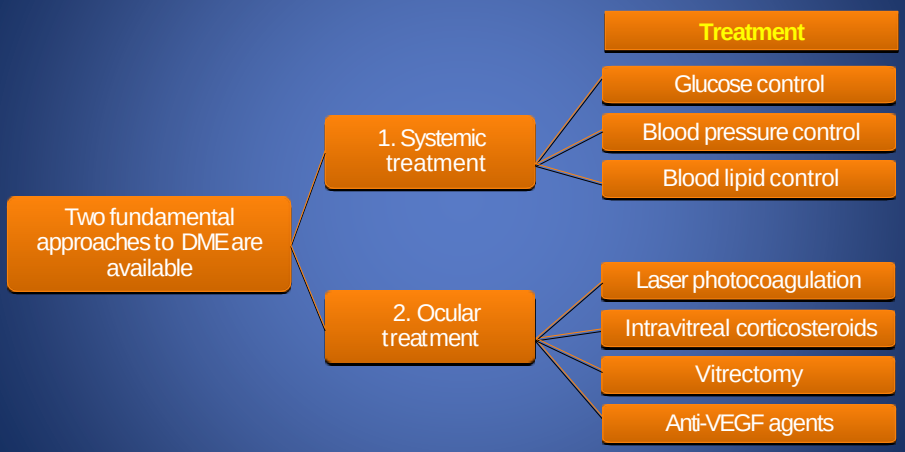
1. National Diabetes Fact Sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed May 2014. 2. Rodbard HW, et al. Endocr Pract 2007;13:4-69

DME patients are at further risk of stroke and cardiovascular disease compared with patients without DR



[a]Age and gender matched diabetes subjects without ophthalmic manifestations, retinal disorders, or vitreous hemorrhage. DME, diabetic macular edema; DR, diabetic retinopathy
Nguyen-Khoa B, et al. BMC Ophthalmol 2012;12:11

Treatment of DME requires a multifactorial approach



DME, diabetic macular edema; VEGF, vascular endothelial growth factor
1. Yam JCS, Kwok AKH. Hong Kong Med J 2007;13:46-60; 2. Moss SE, et al. Ophthalmology 1994;101:1061-70

Approved pharmacologic treatments for DME: Ranibizumab

Ranibizumab (LUCENTIS®)[1]

- Specifically designed for intraocular use
- Monoclonal antibody fragment, maximizing biologic activity while minimizing systemic exposure
- Inhibits the action of VEGF in the retina to decrease vascular permeability and edema
- Efficacy and safety profile supported by several clinical trials (e.g. RIDE, RISE, RESTORE, RETAIN)[2-4]
- Approved by FDA in 2017 and then over 100 countries worldwide[5]
- Very favorable safety profile

DME: diabetic macular edema, VEGF v
1. Novartis. Lucentis SmPC 2014; 2. Brown DM, et al. Ophthalmology 2013;120:2013:22; 3. Schmidt-Erfurth U, et al. O
4. Prünte C. American Academy of Op

Pegaptanib (Macugen)

- Was the first anti VEGF treatment (specific to the 165 isoform of VEGF A) to show a favourable effect on diabetic macular oedema.
- Different doses of Macugen (0.3mg, 1mg, 3mg)

Bevacizumab (Avastin)

A full-length humanized antibody to VEGF-A that binds all VEGF isoforms.

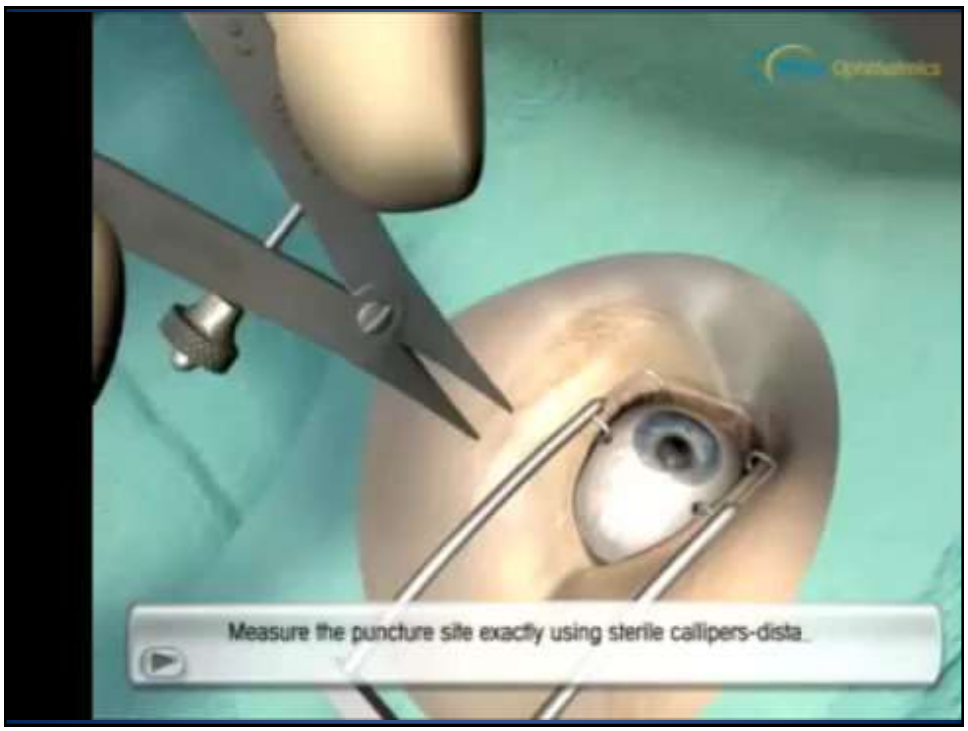
1.25 and 2.5mg

Aflibercept (Eylea)
2mg

A soluble VEGF receptor fusion protein that binds to all isoforms of VEGF-A as well as placental growth factor. It has a higher binding affinity compared to that of ranibizumab and bevacizumab and thus potentially has a longer duration of action.

Vsiqq (brolucizumab)

- Vsiqq 6mg provides a robust visual gains and less disease activity with over 50% of patients on a 12 w dosing interval after the initial loading dose.
- Vsiqq 6 mg provides a superior anatomical outcomes in terms of superior reduction in CST and greater retinal fluid resolution(IRF,SRF,&sub RPE)



Which drug to use

- Better vision
- Better drying
- Longer acting
- Minimal side effects
- Cost of the drug

10% CST AND 5 LETTER RULE

- ❖ Worsening: CST increased by10%, 5 letter reduction in VA
- ❖ Improvement: CST decreased by 10%, VA improved by 5 letters.

Injection protocols

1. Monthly treatment.
2. PRN (PRO RE NATA) protocol.
3. Treat and extend.

MONTHLY TREATMENT

- The phase 3 RISE and RIDE clinical trials and the phase 3 VIVID and VISTA trials established the superiority of anti-VEGF drugs over focal laser for the treatment of eyes with DME.
- These clinical trials were designed to establish treatment superiority over focal laser and were modeled after earlier studies in which intravitreal injections of an anti-VEGF agent were administered monthly for treatment of exudative age-related macular degeneration (AMD).

Advantages

There are several advantages to treating eyes with center-involving DME with monthly intravitreal injections regardless of the presence or absence of edema.

- Rapid visual acuity improvement and that the gain is maintained for at least 3 years.
- Visual acuity continues to improve for up to 1 year before stabilizing.
- The other main benefit of monthly treatment is regression of diabetic retinopathy (DR). With monthly treatment, 35.9% to 47.0% of patients experienced regression of 2 or more steps in DR severity score, and 13.2% to 15.0% had regression of 3 or more steps in retinopathy severity.

Disadvantages

- Financial cost to patients and insurers .
- Patients must dedicate several hours each month to traveling to the office, and family members often share this burden, further increasing indirect costs.
- In addition, the repeated injections carry a low but real risk of endophthalmitis and other complications related to the injection itself.

PRN

- Continue ttt until:

1. VA reached 20/20.
2. OCT central subfield thickness <250.
3. Less than 10% change in OCT thickness Since last ttt.
4. Less than 5 letter Change in VA since last ttt

Then as and when required

PRN

- Restart ttt:

- Drop of VA 10 or more letters.
- Centeral subfield thickness>250.

Advantages of PRN

Robust VA gain followed by stability with substantial reduction in number of injections.

TREAT AND EXTEND

- Monthly injections till stability.
- Follow up gradually extended by 1-2 weeks based on CST and BCVA.
- Maximum extension is 12 weeks.
- If worsening seen , reduce follow up period.
- Minimum is 4 weeks

In treat and extend regimen the patient receives injection at every visit

Advantages

- A treat-and-extend regimen has several potential advantages. Unlike with a PRN schedule, the clinician does not have to wait until macular edema is worse before treating the patient. Chronic macular edema can lead to irreversible vision loss, so preventing recurrence of edema can potentially preserve visual acuity in the long term, although studies are needed to confirm this.
- A treat-and-extend regimen can also reduce the number of office visits without sacrificing visual acuity.

The main difference between TAE and PRN IS:

- Treat and extend is proactive.
- PRN regimen is reactive.

Anti-VEFG side effects

- The most common side effects are… conj hge, eye pain, vitreous floaters.
- Thromoembolic events. Incidental?

Serious adverse events (less than 1%)

Endophthalmitis

Retinal detachment

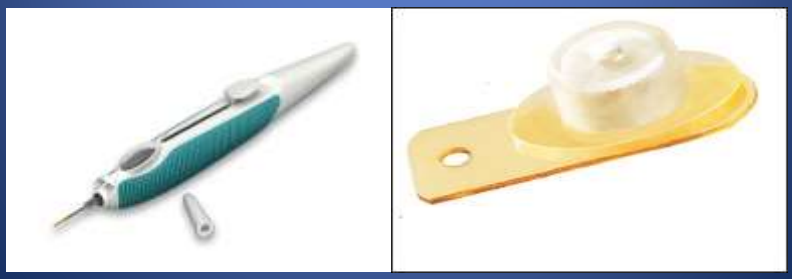
Traumatic cataract

INTRAVITREAL STEROID TREATMENT

IVTA

- Three intravitreal TA injection doses of 1, 4 and 20 mg have been used in clinical practice, with 4 and 20 mg considered the most effective treatment doses.

- The **lLUVIEN (or retisert)** sustained-release fluocinolone acetonide (FA) implant device - a new local via subtenon's or intravitreal injection drug, has been shown to be effective in the treatment of refractory DME and uveitis



- **OZURDEX** is a dexamethasone sustained-release biodegradable drug.

- Intraocular OZURDEX has been shown to be long-acting and effective for the treatment of persistent refractory macular edema caused by branch and central vein occlusion, DME, as well as non-infectious uveitis in phase III clinical trials

Steroid side effects

- Cataract
- IOP spike

so indicated only in refractory edema to AntiVEGF esp. in pseudophakics


Thank you