Novartis Symposium

Evolution of Treatment in DME

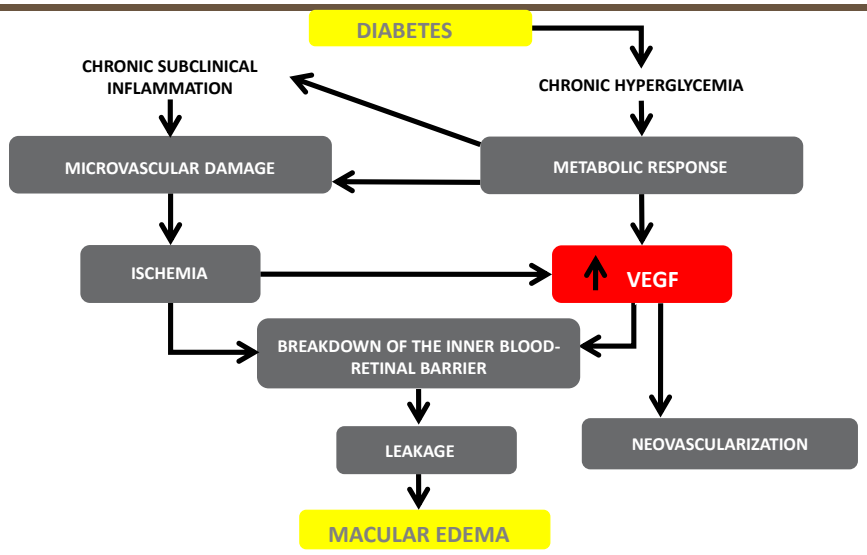
Ahmed Souka
Novartis Symposium

AOS 2019

DME

- Pathophysiology of the disease

Role of VEGF in the pathophysiology



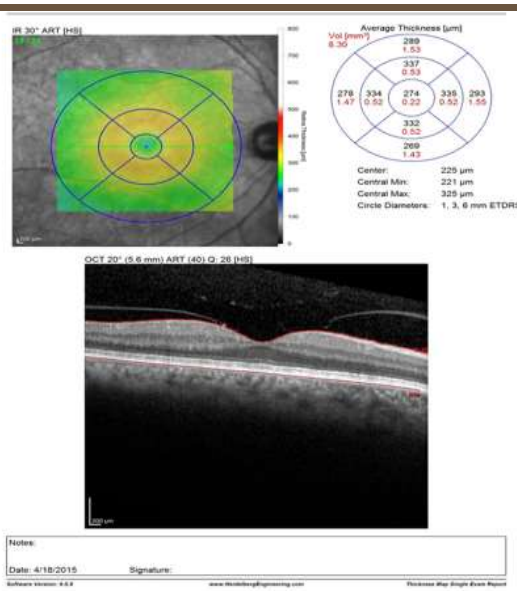
Boyer DS, ADA 71st Scientific sessions, San Diego, California, 2011

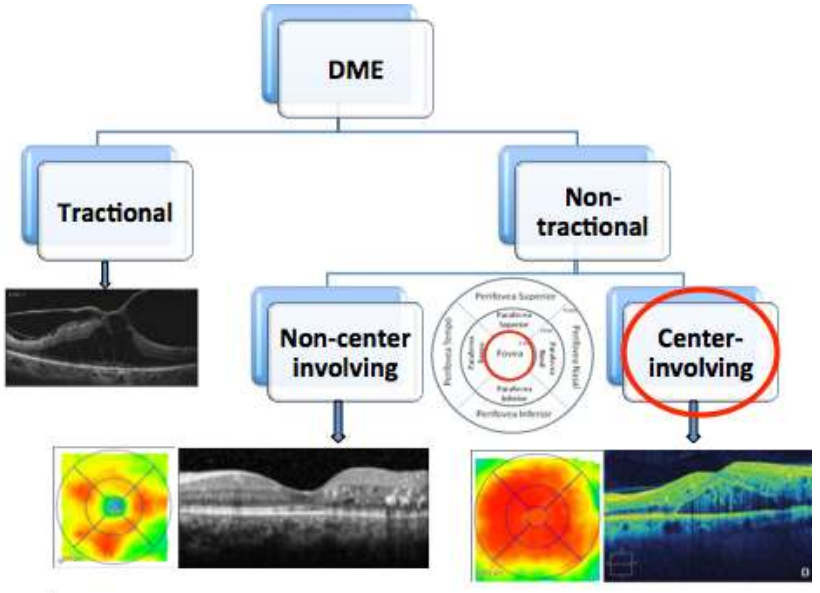
DIAGNOSIS OF DME

OCT is the Tool

Fluorescein Angiography is rarely needed

Normal OCT Appearance





Medical Management of DME

Laser Photocoagulation

Steroids Injections

ANTI VEGF Injections

Medical Management of DME

Laser Photocoagulation

Steroids Injections

ANTI VEGF Injections

Laser photocoagulation

- **Laser photocoagulation**[1,2]
  - It was the standard treatment between 1985 and 2010 — as it helps to slow fluid leakage and **reduces** the amount of fluid in the retina (Macular Edema).[1,2]
  - **Stabilizes /** prevents further vision loss.[1,2]
  - Recommended for Clinically significant Macular Edema without centre involvement or with centre involvement in mild cases.[3]

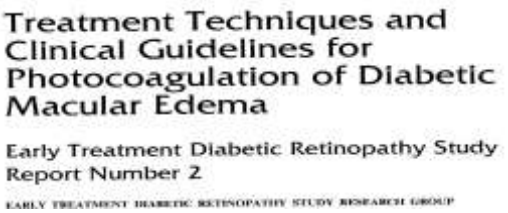
1. Early Treatment Diabetic Retinopathy Study research group. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985; 103:1796–806
2. Diabetic Retinopathy Clinical Research Network. Ophthalmology 2008; 115: 1447–9, 1449 e1–10
3. Royal college of ophthalmologists. Diabetic Retinopathy guidelines Dec 2012

DME: diabetic macular edema

First Publications

1985

ETDRS study



Treatment Techniques and Clinical Guidelines for Photocoagulation of Diabetic Macular Edema

Early Treatment Diabetic Retinopathy Study Report Number 2

EARLY TREATMENT DIABETIC RETINOPATHY STUDY RESEARCH GROUP

Arch Ophthalmol 1985; 103:1796–806

EDTRS classification

- The classification was mainly based on clinical diagnosis to detect thickening

- FA was only useful to detect the type of leakage,
- whether it was focal or diffuse to define type of laser being used.

- For focal edema, focal laser was applied to the site of leakage,
- whereas in diffuse type a grid laser was performed.

CSME Criteria for Laser treatment of DME : ETDRS 1

Figure 5-7 Clinically significant macular edema (CSME). Retinal edema located at or within 500 µm of the center of the macula. *(Courtesy of the ETDRS.)*

CSME Criteria for Laser treatment of DME : ETDRS 2

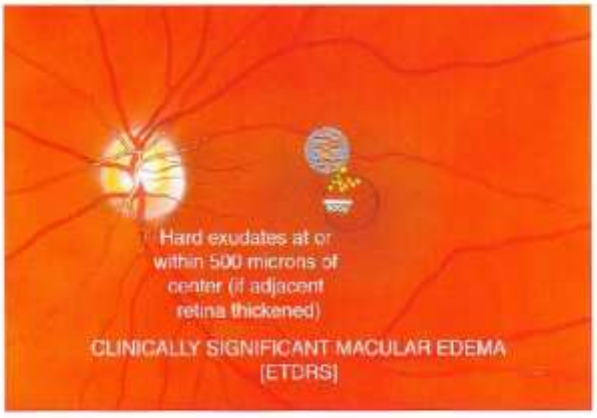


Figure 5-8 CSME. Hard exudates at or within 500 μm of the center of the macula if associated with thickening of the adjacent retina. *(Courtesy of the ETDRS.)*

CSME Criteria for Laser treatment of DME : ETDRS 3

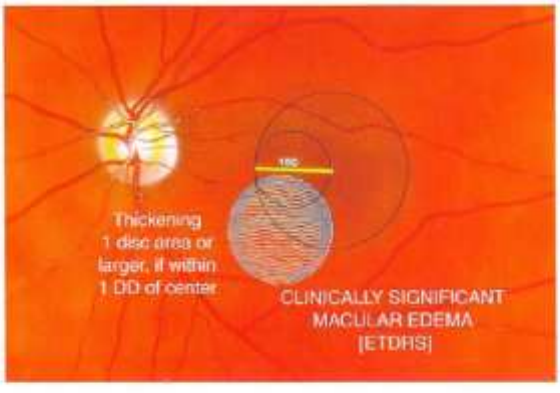


Figure 5-9 CSME. A zone of thickening larger than 1 disc area if located within 1 disc diameter of the center of the macula. *(Courtesy of the ETDRS.)*

Response to Laser : Focal vs Diffuse

- The ETDRS found NO difference in the response to laser photocoagulation when comparing eyes with focal leakage or eyes with ‘ intermediate to diffuse’

- Similar results with photocoagulation were reported by Blankenship et al in another large scale study.

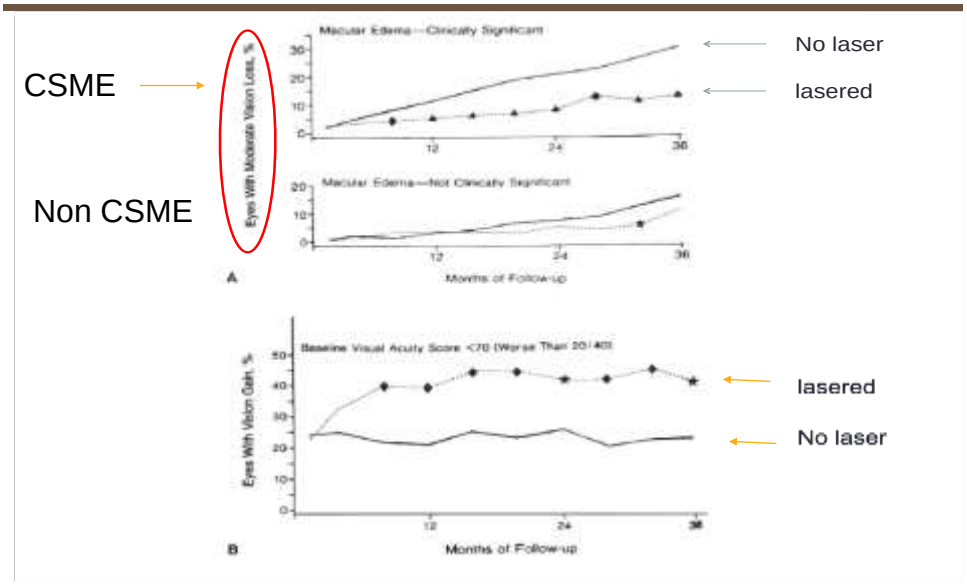
Why was Laser beneficial? **less drop in Vision**

- 50% reduction of patients who develop moderate to severe visual loss

- 2X number of patients who can reach 6/12

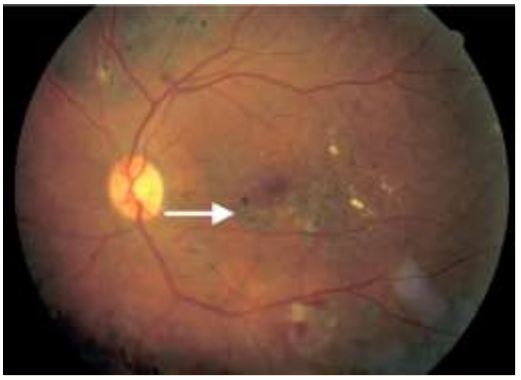
- Doing Laser for DME cases was considered beneficial?

Results of the ETDRS Trial

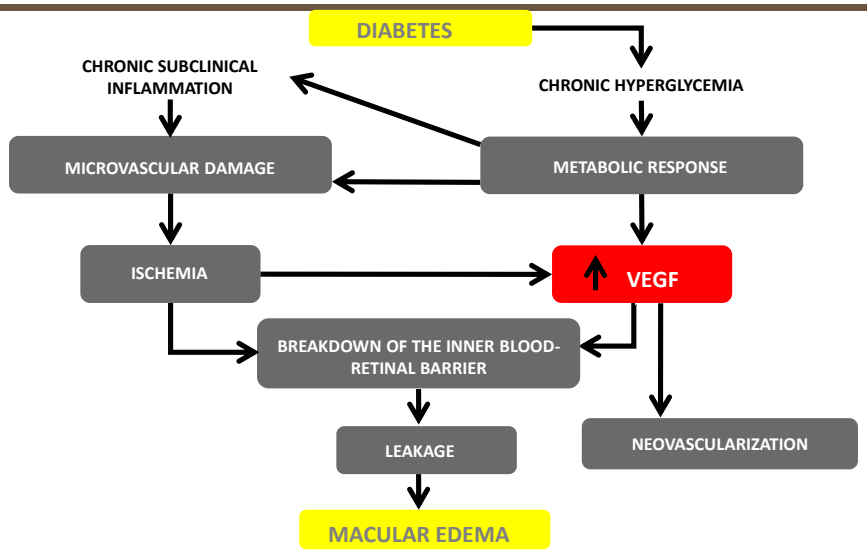


Limitations and complications of laser

- **Complications**[4,5]
  - Foveal burn
  - Central visual field defects
  - Colour vision abnormalities
  - Retinal fibrosis
  - Spread of laser scars



Role of VEGF in the pathophysiology



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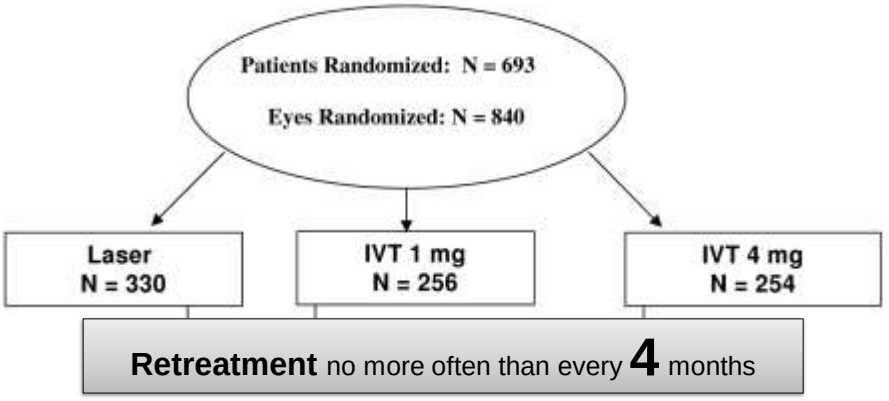
Medical Management of DME

Laser Photocoagulation

Steroids Injections

ANTI VEGF Injections

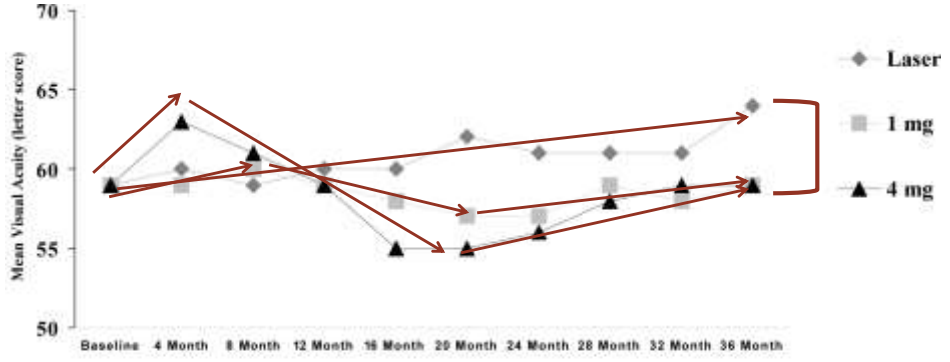
Protocol B: IVTA vs Laser study *



* DRCR.net study group

Results of DRCR PROTOCOL B : IVTA vs LASER

VA change in 3 years



Number of eyes examined at each visit

Laser	330	311	299	286	263	251	272	229	164	115
1 mg	256	241	231	230	214	212	221	175	137	93
4 mg	254	244	226	221	208	196	204	177	127	98

Conclusions : **Steroids** Injection for DME

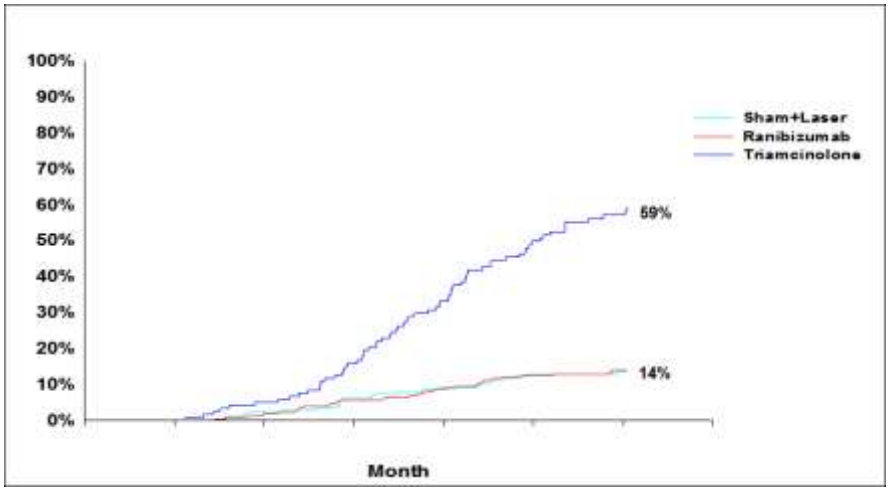
- There was no **long-term** benefit of intravitreal triamcinolone relative to focal/grid photocoagulation for patients with DME
- Rather, visual acuity outcomes slightly favored the laser group compared with either of the two triamcinolone groups.

IOP elevation in Steroid injections Protocol B

	Laser	TA 1 mg	TA 4 mg
>10 mmHg rise in IOP @ anytime in 3 yrs	4 %	18 %	33 %
IOP>30 mmHg	1 %	9 %	21 %
% on IOP lowering drugs @ end of 3 yrs	3 %	2 %	12 %
Glaucoma procedure	0 %	0 %	1.5 %

Cataract in Steroid injections Protocol I

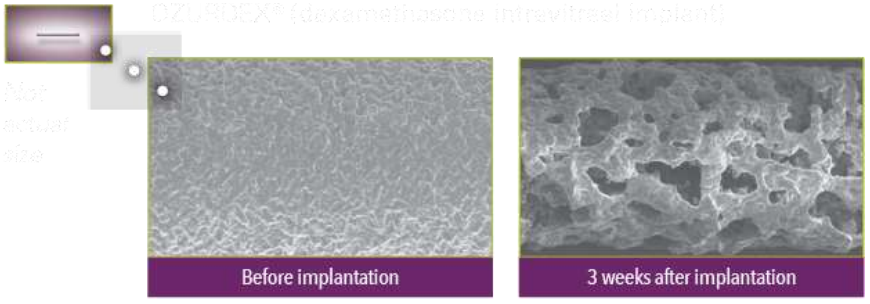
Cumulative Probability of Cataract Surgery



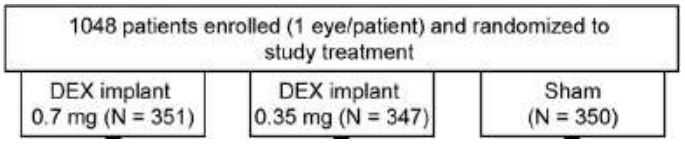
Intravitreal Steroid Sustained-release Implants

Ozurdex Implant

Ozurdex (Allergan)



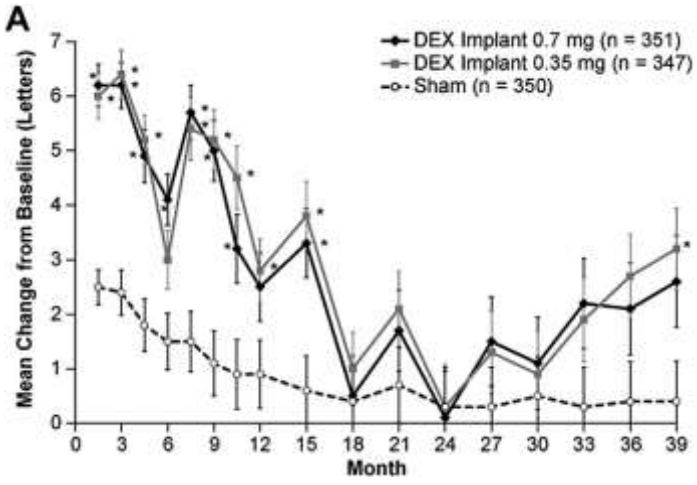
MEAD study: 3 years / DEX implant



Retreatment no more often than every 6 months

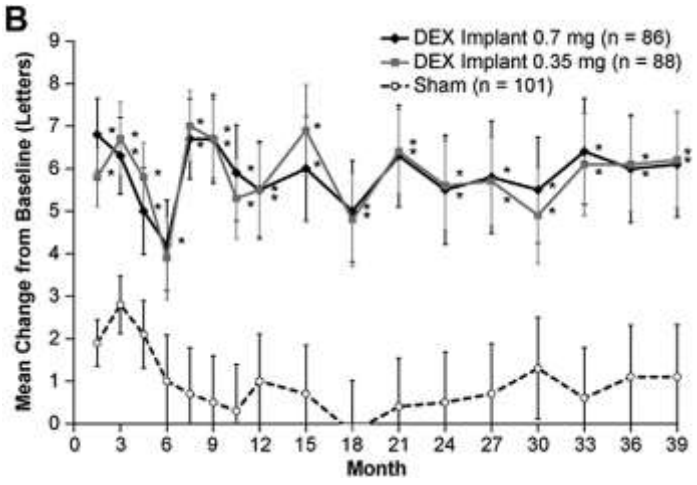
MEAD study (whole study)

Mean change VA



MEAD study (Pseudophakic only)

Mean change VA: Pseudophakic



Cataract surgery incidence : MEAD / DEX Implant

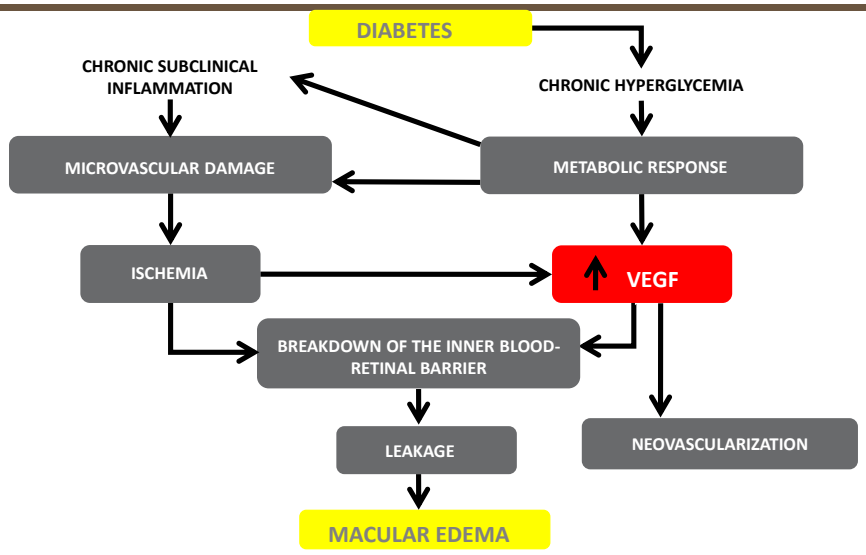
- DEX 0.7 mg → 59.2%
- DEX 0.35 mg → 52.3%
- Sham → 7.2%

Steroids : Why consider it ?

- Cheap (but not implants)
- Result temporary for few months
- High incidence of cataract (59%)
- Drop of vision after few months
- Glaucoma (Common complication)

- How does Anti VEGF compare to Steroids??

Role of VEGF in the pathophysiology



Boyer DS, ADA 71st Scientific sessions, San Diego, California, 2011

Medical Management of DME

Laser Photocoagulation

Steroids Injections

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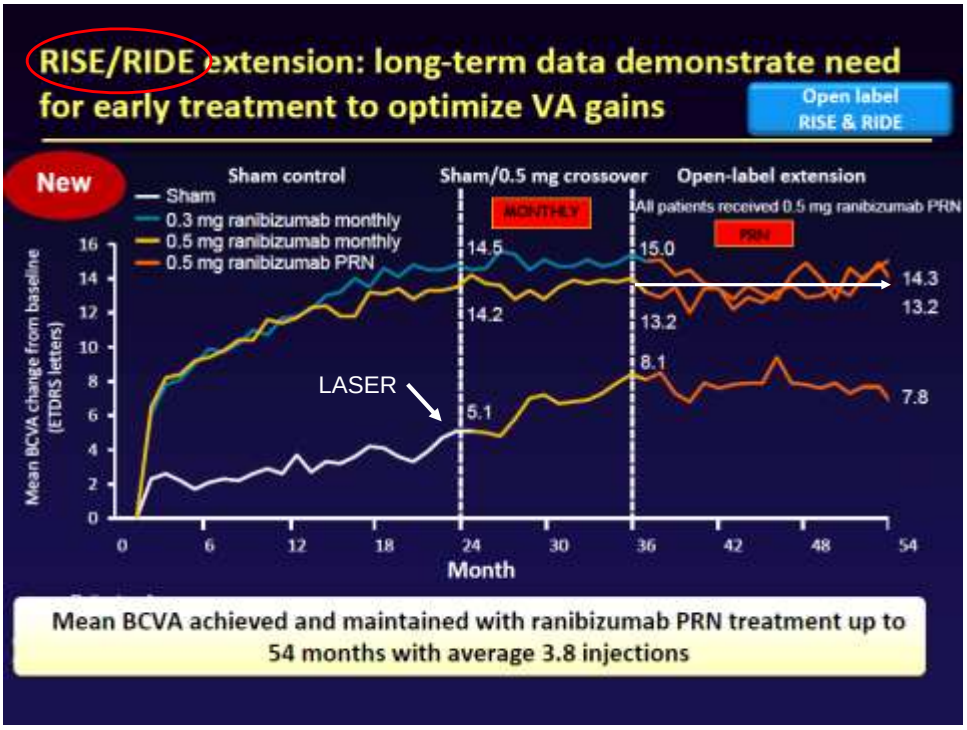
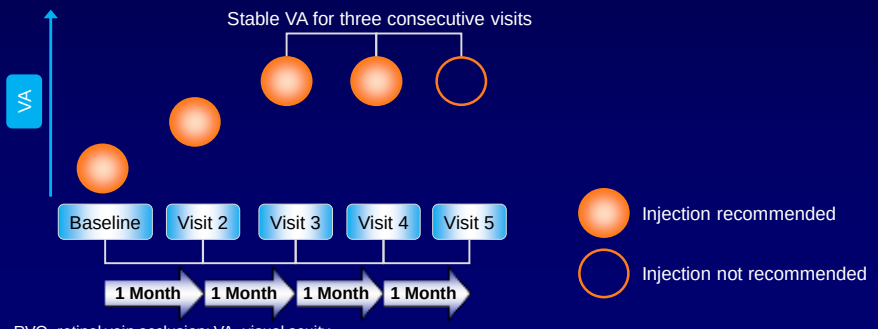


Evolution of Anti VEGF drugs Protocols

- Anti VEGF Management Protocol
  - VA Based ?
  - OCT Based ?

Monthly injections given & suspended when:

- Monthly treatment until **maximum VA** is achieved then observe.
  - **'Maximum VA' is defined as VA stable for three consecutive monthly assessments while on ranibizumab treatment**

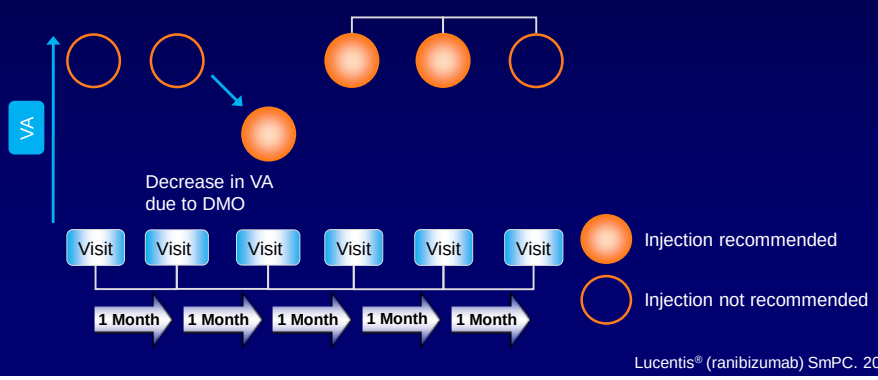


RVO, retinal vein occlusion; VA, visual acuity
wAMD, wet age-related macular degeneration

Lucentis® (ranibizumab) SmPC. 2012

Retreatment is initiated when:

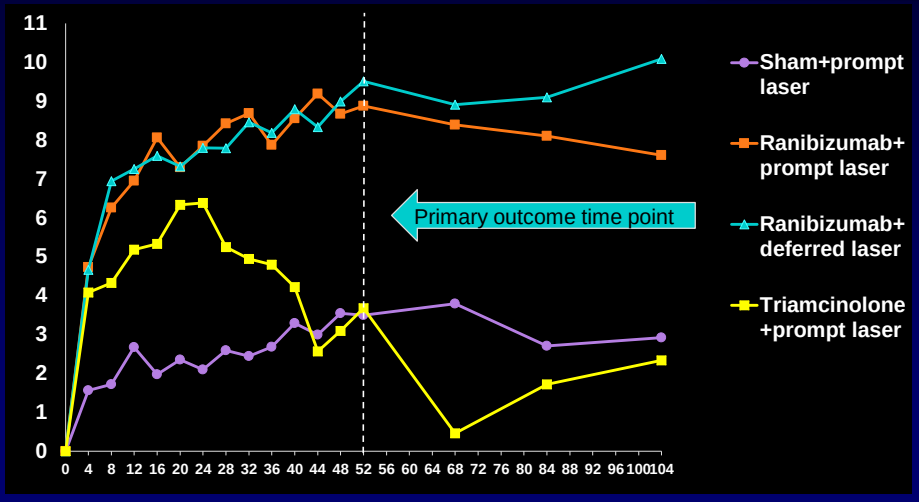
- Injection resumed if **loss of VA due to DME**
  - **Monthly injections administered until stable vision for three consecutive monthly assessment while on ranibizumab treatment**



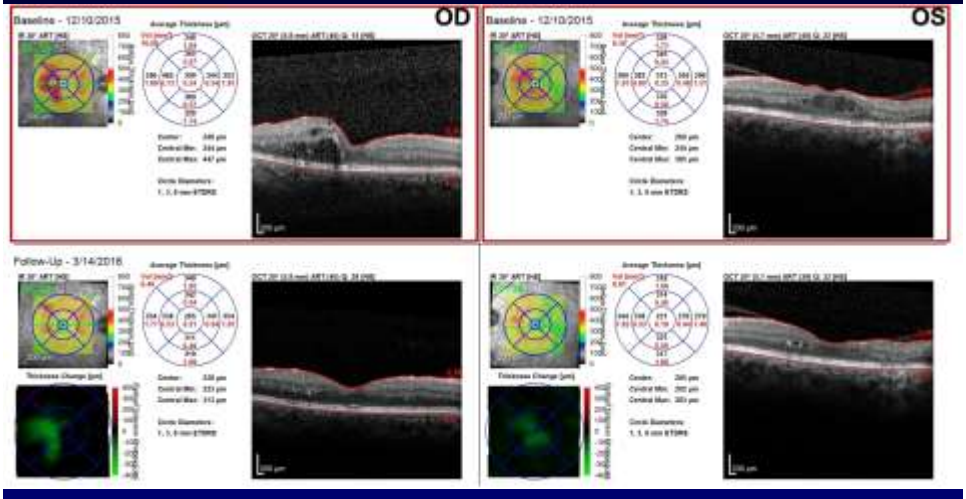
Lucentis® (ranibizumab) SmPC. 2012

Change in VA from baseline

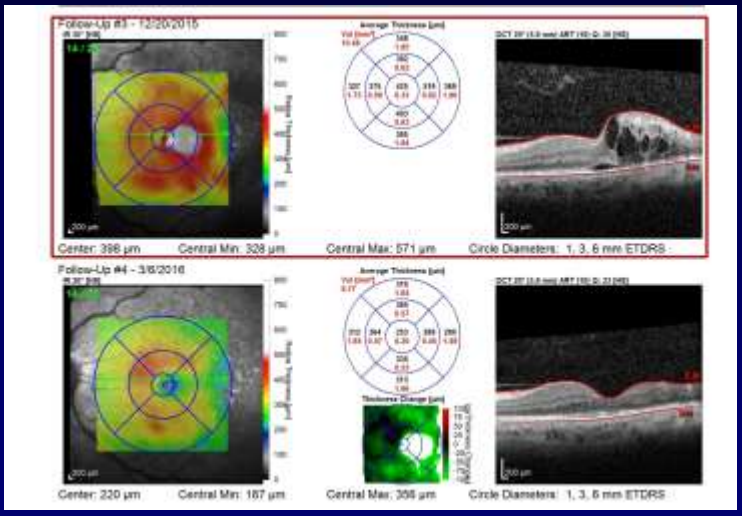
2 year results



➢ After 3 injections of anti-VEGF both eyes

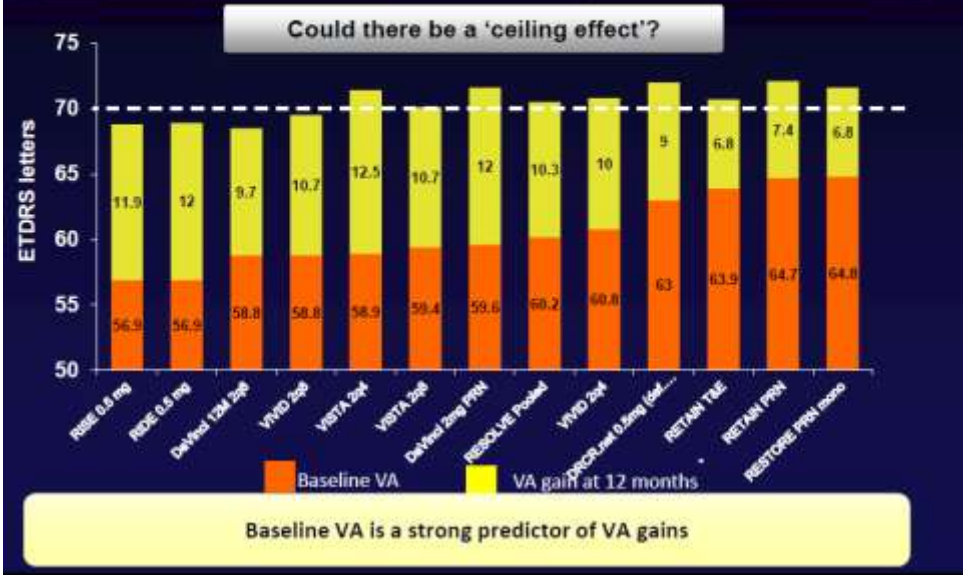


➢ **Before & After 3 injections = VA 6/12**



Baseline VA is a strong predictor of VA gains

No cross-trial comparisons unless studies are prospectively designed in a head-to-head manner



Medical Management of DME

Laser Photocoagulation

Steroids Injections

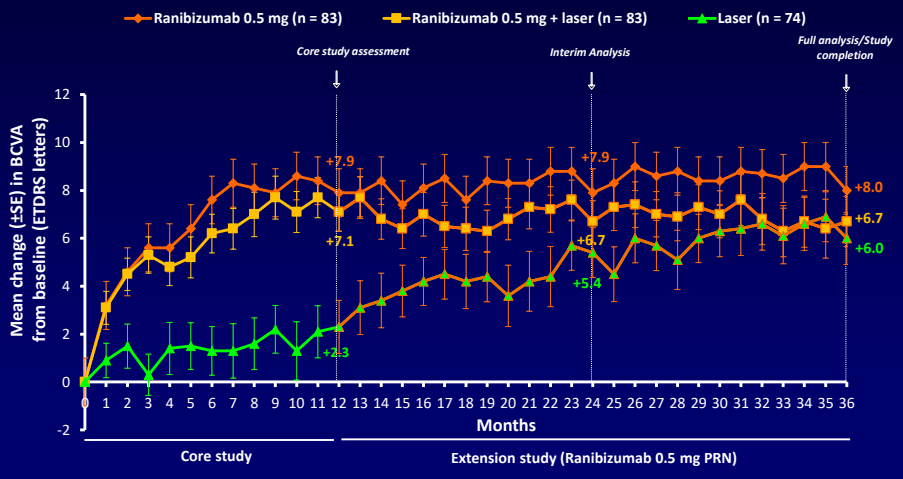
ANTI VEGF Injections

Why Not Use both Anti VEGF & Laser ??

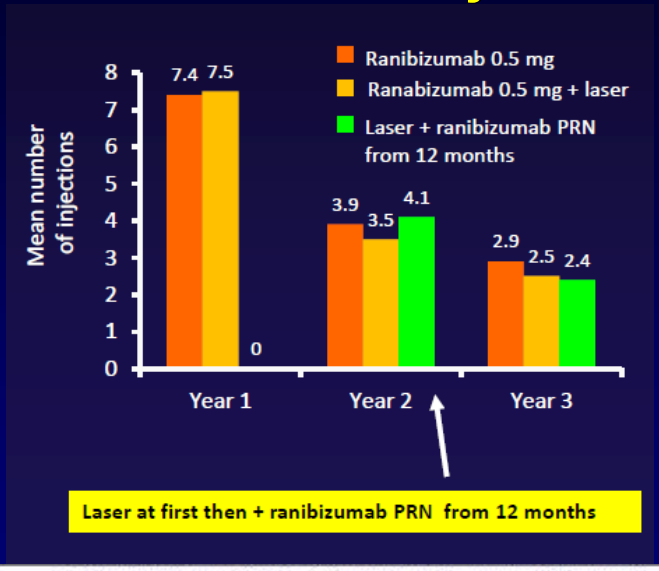
- **Adding laser may benefit??**
  - **Improve vision ??**
  - **Reduce injections number??**

Mean change in BCVA: RESTORE

3 year results



Reduced need for injections ??



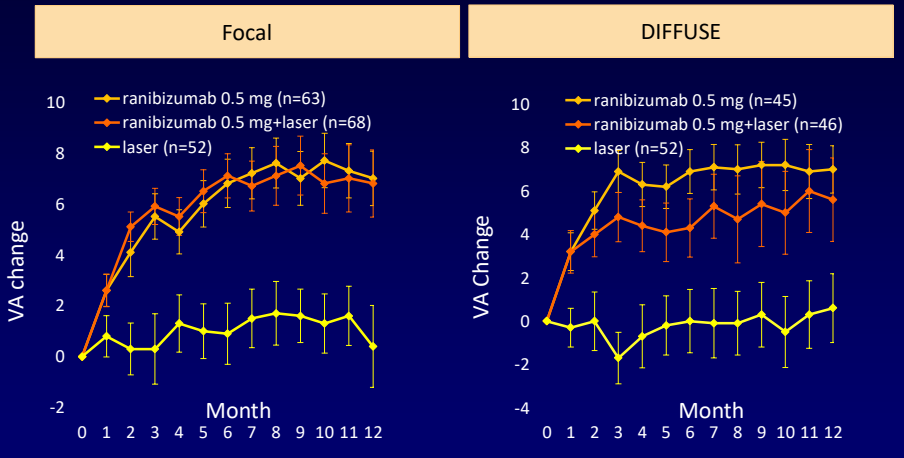
19% to 25% of patients did not require any ranibizumab injections during the extension study.

Changes in How we Perceive DME

Taboos Broken

- **Focal vs Diffuse DME:**
  - **Why?**
    - **Focal Laser vs Grid Laser**
    - **Anti VEGF injections ?**

Mean change in BCVA from baseline to Month 12 by baseline DME type



Full analysis set/LOCF
BCVA: best-corrected visual acuity; VA: visual acuity; LOCF: last observation carried forward

Mitchell P et al. Ophthalmology 2011;118:615-625

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Changes in How we Perceive DME

Taboos Broken

- CSME or Not ?
  - Meaningless in the era of OCT
  - Only to Perform Laser (Rare)
  - The Question is :
    - CiME vs non-CiME

Changes in How we Perceive DME

Taboos Broken

NEW Generations do NOT understand why we are still mentioning CSME,

or considering Focal vs Diffuse,

or ordering FLA (no need)

Decreasing use of FA in managing DME

- IN 1998 audit of DME management, only 19.5% of British ophthalmologists treating DME with focal laser obtained a FA before treatment.
- In a 2007 study from the DRCR.net, 50% of eyes were managed without FA.

- DRCR quote: ' Any system of classifying DME that relies on FA will suffer from inutility by the majority of clinicians who avoid this ancillary study in their management of the condition.

This trend to use FA may change if some evidence of usefulness in treating and predicting outcome is discovered'

Changes in How we Perceive DME

Taboos Broken

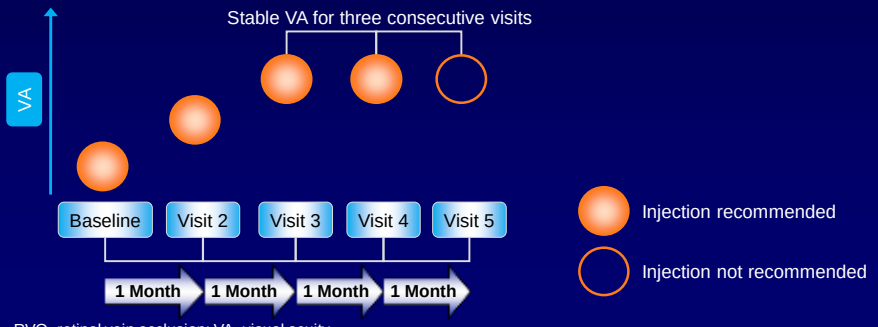
- New Questions:
  - Which Drug ?
  - When Do we Stop?
  - Is it going to Last Forever …….

DRCR Protocol T

- Comparing drugs
- Avastin & Lucentis & Eylea
- Included changes in OCT to the stable point of Vision in Follow up

Monthly injections suspended when:

- Monthly treatment until maximum VA is achieved
- If changes in OCT >10% , then continue injection
- 'Maximum VA' is defined as VA stable for three consecutive monthly assessments while on ranibizumab treatment

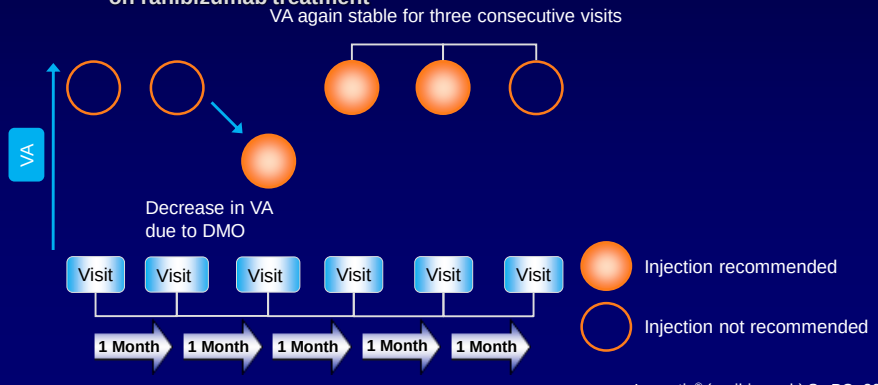


RVO, retinal vein occlusion; VA, visual acuity
wAMD, wet age-related macular degeneration

Lucentis® (ranibizumab) SmPC. 2012

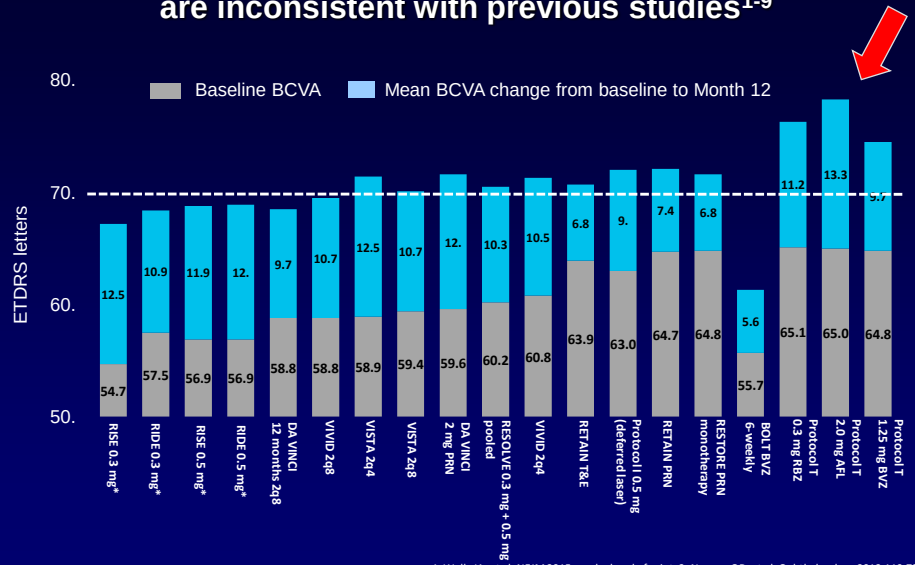
Retreatment is initiated when:

- **Injection resumed if loss of VA due to DME**
  - Monthly injections administered until stable vision and
  - NO change in OCT for three consecutive monthly assessment while on ranibizumab treatment



Lucentis® (ranibizumab) SmPC. 2012

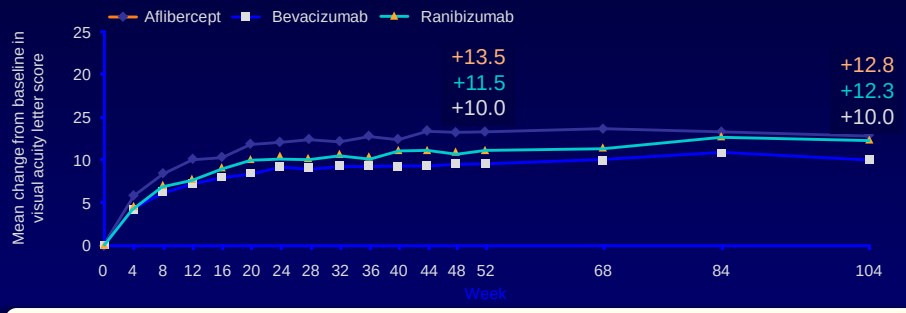
Mean 12-month visual acuity scores in Protocol T are inconsistent with previous studies[1-9]



Collation of available studies – study designs may vary; *2-year data

1. Wells JA, et al. NEJM 2015, epub ahead of print; 2. Nguyen QD, et al. Ophthalmology 2012;119:789-801
3. Do DV, et al. Ophthalmology 2012;119:1658–65; 4. Do DV, et al. Ophthalmology 2011;118:1819-26; 5. Korobelnik JF, et al. Ophthalmology 2014 epub ahead of print; 5. Massin P, et al. Diabetes Care 2010;3:2399–405; 6. Prünte C, et al. ARVO 2014 ID 1700; 7. DRCR.net, et al. Ophthalmology 2010;117:1064–77; 8. Mitchell P, et al. Ophthalmology 2011;118:615–25; 9. Michaelides M, et al. Ophthalmology 2010;117:1078-8

Similar VA gains in overall population between aflibercept and ranibizumab at 2 years



At Year 1, the improvement was greater, but not clinically meaningful, with aflibercept than with the other two drugs.[1] At Year 2, the difference in VA gain between aflibercept and ranibizumab was **no longer significant** (p = 0.47), indicating that a dose of ranibizumab that is 60% of the 0.5 mg ex-U.S. approved dose produced **equivalent VA gains** over 2 years to the full aflibercept 2.0 mg dose.[2]

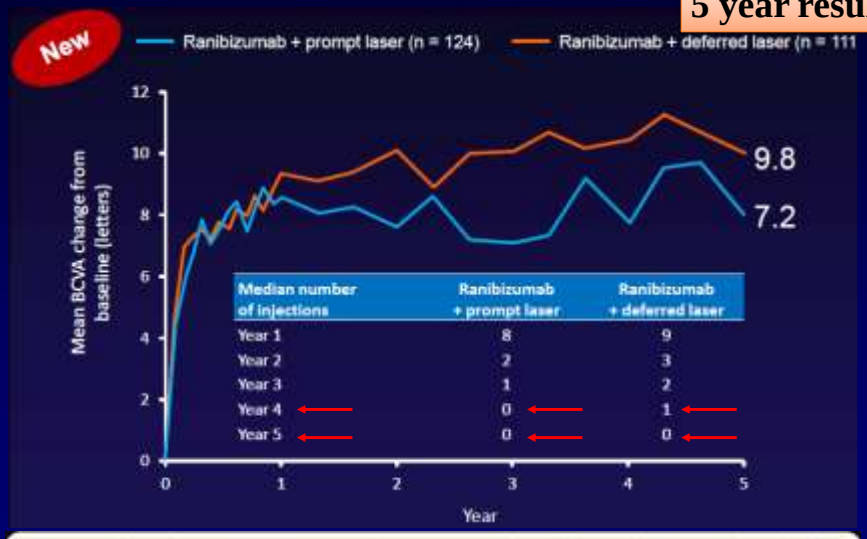
1. Wells JA, et al. NEJM 2015;372:1193-203 2. Wells JA, et al. . Ophthalmology 2016;XX:1-9 http://dx.doi.org/10.1016/j.ophtha.2016.02.022

Updates in Treatment

- Are we going to inject forever ?
  - 5 Years Protocol I DRCR

Change in VA from baseline

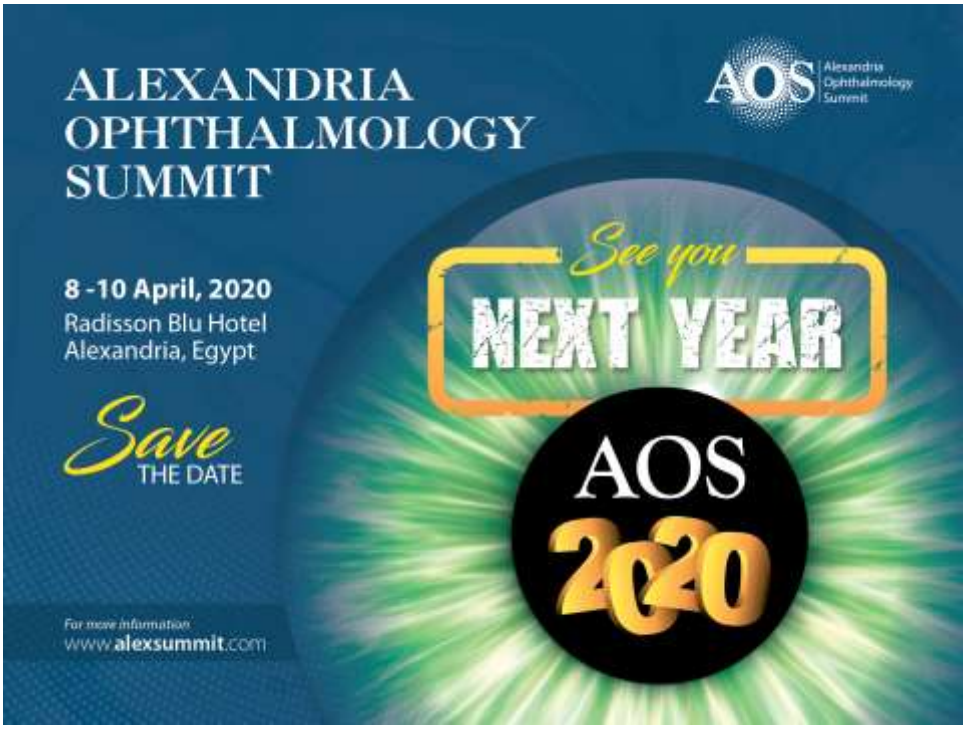
5 year results



5-year data demonstrate sustained response with ranibizumab PRN with marked reduction in injection requirements over time

Take Home message

- Anti VEGF is the Best modality
- Laser is Better than NO treatment
- Laser does not ADD to Anti VEGF
- Depend on VA and consider OCT changes
- All Drugs are effective
- DME will not last Forever
- Nearly ALL DME will be gone in 3-5 Y
- Those who inject will end up BETTER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