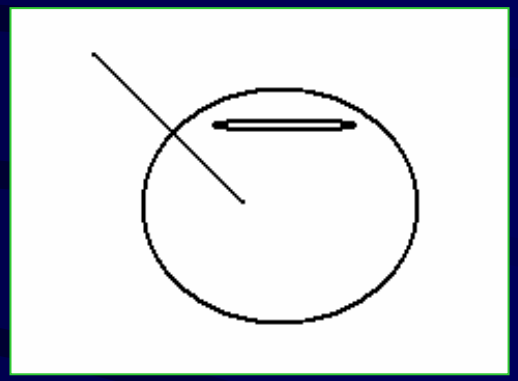
Anti-VEGF drugs & CATT Results in AMD



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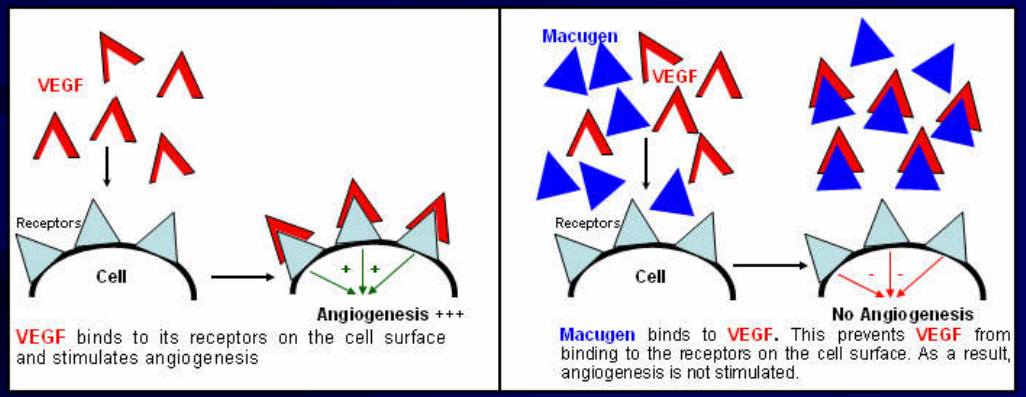
Vascular Endothelial Growth Factor

- Napoleone Ferrara at Genentech 1989 identified & cloned the gene
- Protein that causes abnormal blood vessels to grow, leak & bleed

VEGF in AMD

- Eyes with AMD have elevated levels of VEGF
- Anti-VEGF drugs work by inhibiting this protein



Advantage over PDT

- Anti-VEGF therapy works equally well across all CNVM types
- Classifying of CNVM as occult/ classic types not crucial

Advantages of anti-VEGF over PDT
Limitations of PDT

- Subretinal scarring
- RPE tears
- RPE atrophy > area of CNVM

The VEGF Family

- VEGF-A, B, C, D & E
- VEGF-A pivotal role in ischaemic & inflammatory diseases

VEGF isoforms

- VEGF isoforms: 121, 145, 165, 183,189, 206
- VEGF165 predominant pathologic isoform

Pathologic neovascularisation

Pathologic vascular permeability

Anti-VEGF Agents

- Pegaptanib Sodium/ Macugen
- Ranibizumab/ Lucentis
- Bevacizumab/ Avastin

Pegaptanib sodium

- Synthesized single-stranded RNA
- Binds only to VEGF 165 & isoforms longer than 165 aminoacids
- Spares the physiological isoform 121

Excellent ocular & systemic safety profile

However,

- In inflammation & angiogenesis proteases cleave VEGF165 and VEGF A isoforms
- Blocking these smaller forms in addition to intact 165 is important

Pegaptanib sodium

- Results have been disappointing
- Leakage reduces after > 4 injections by which time scarring +
- Vision improvement is infrequent

VISION Study

Macugen

Macugen reduces the probability of vision loss over a year

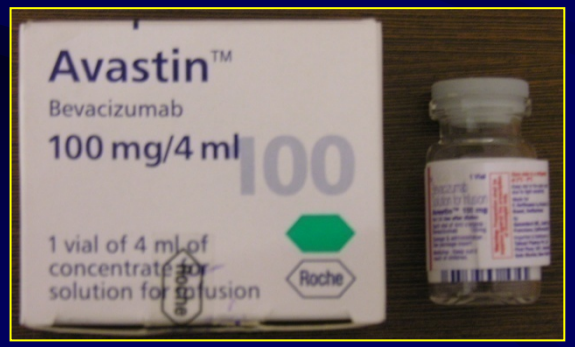
moderate loss:	by 15%
severe loss:	by 50 %

Avastin & Lucentis

- Both are proteins genetically modified from murine monoclonal antibody against VEGF
- Block all biologically active forms of VEGF
- Differ in their size & affinity for VEGF

Bevacizumab (Avastin)

- Full-length, humanized monoclonal antibody against VEGF
- 2 binding sites for VEGF
- Despite its size penetrates the rabbit retina though not RPE and choroid



Ranibizumab (Lucentis)

- A recombinant humanized monoclonal antibody antigen-binding fragment (Fab)
- Has a single affinity-matured binding site for VEGF

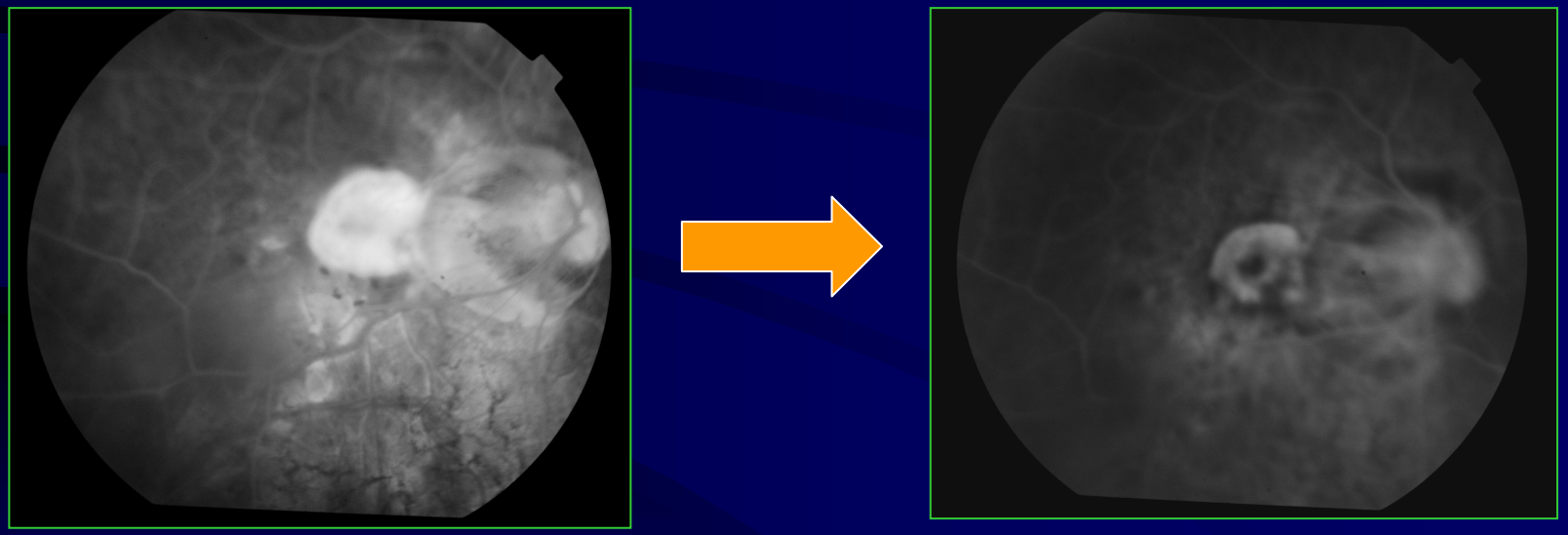
Trials

Lucentis

- MARINA Trial: Minimally classic / occult CNVM
- Anchor Trial: Classic CNVM
- Focus Trial: compared with PDT+anti-VEGF
- PRONTO study: OCT changes

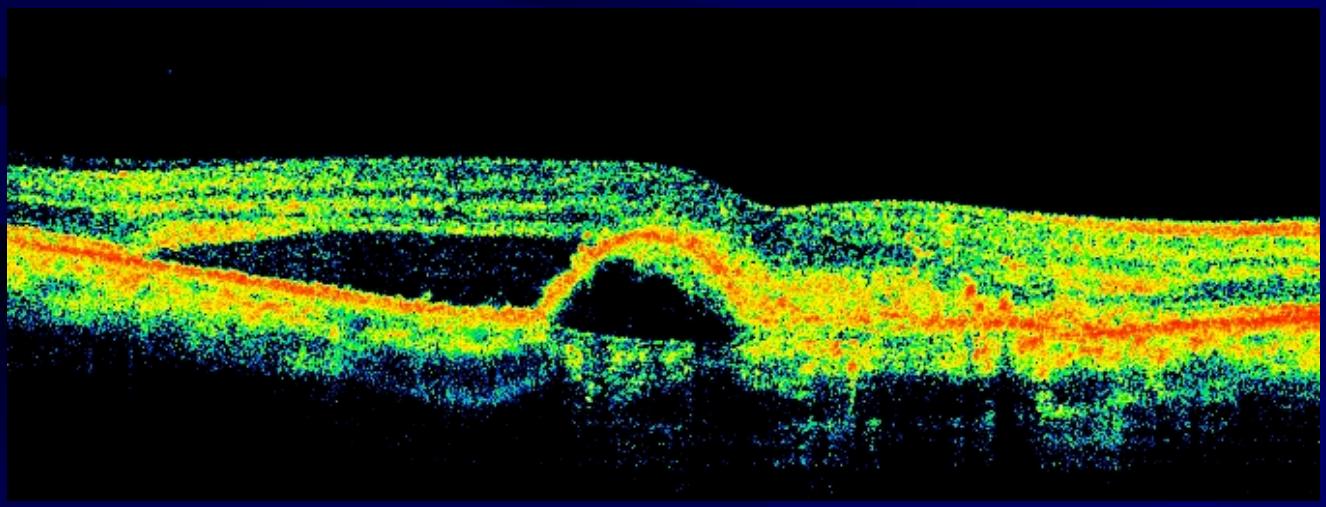
Luvastin monotherapy
Typical response

- Small classic CNVM

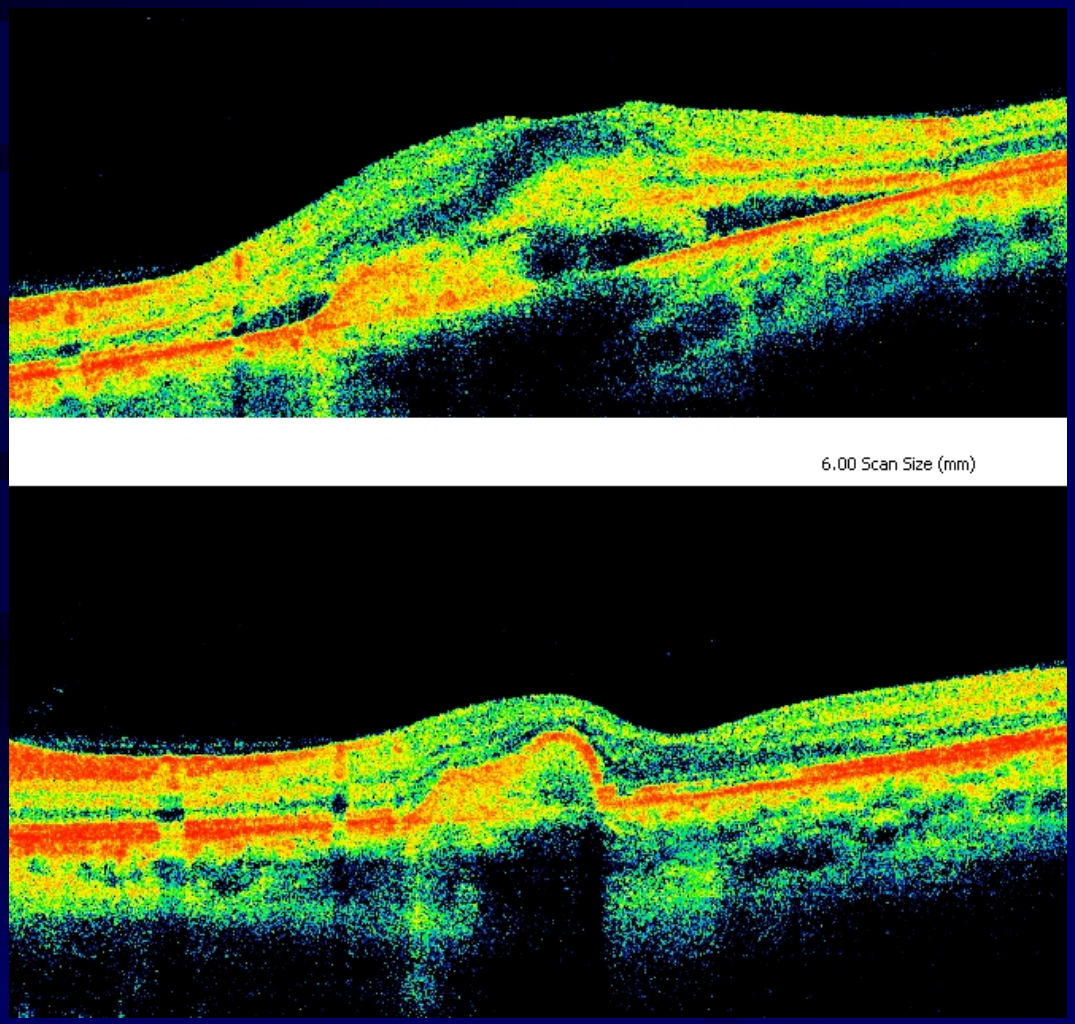


OCT inseperable part of anti-VEGF therapy

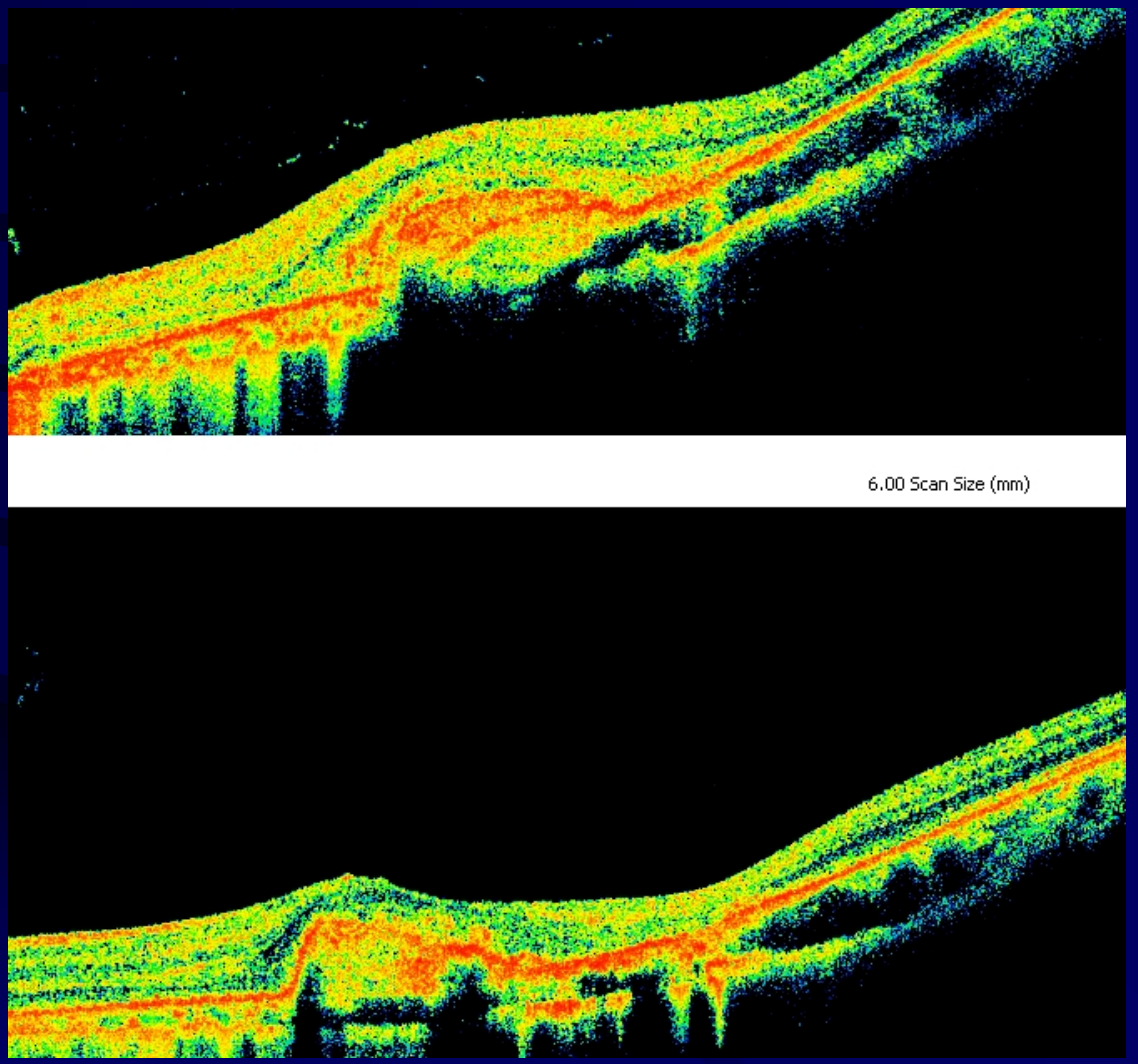
- Identifies CNVM
- Find, Localize and Quantify fluid collections
- Form of fluid: cystoid edema, detachment
- Monitor response

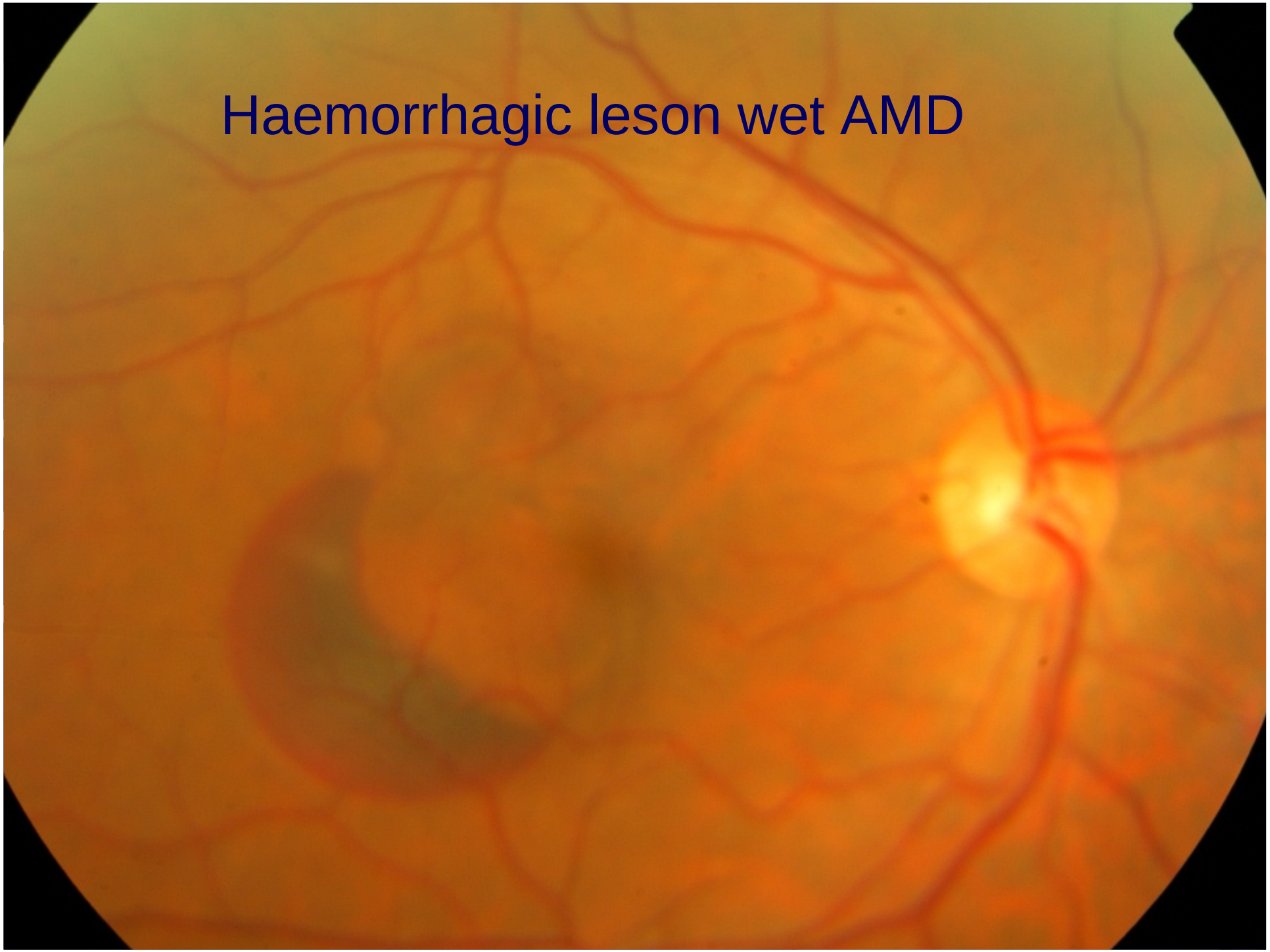


Response to anti-VEGF

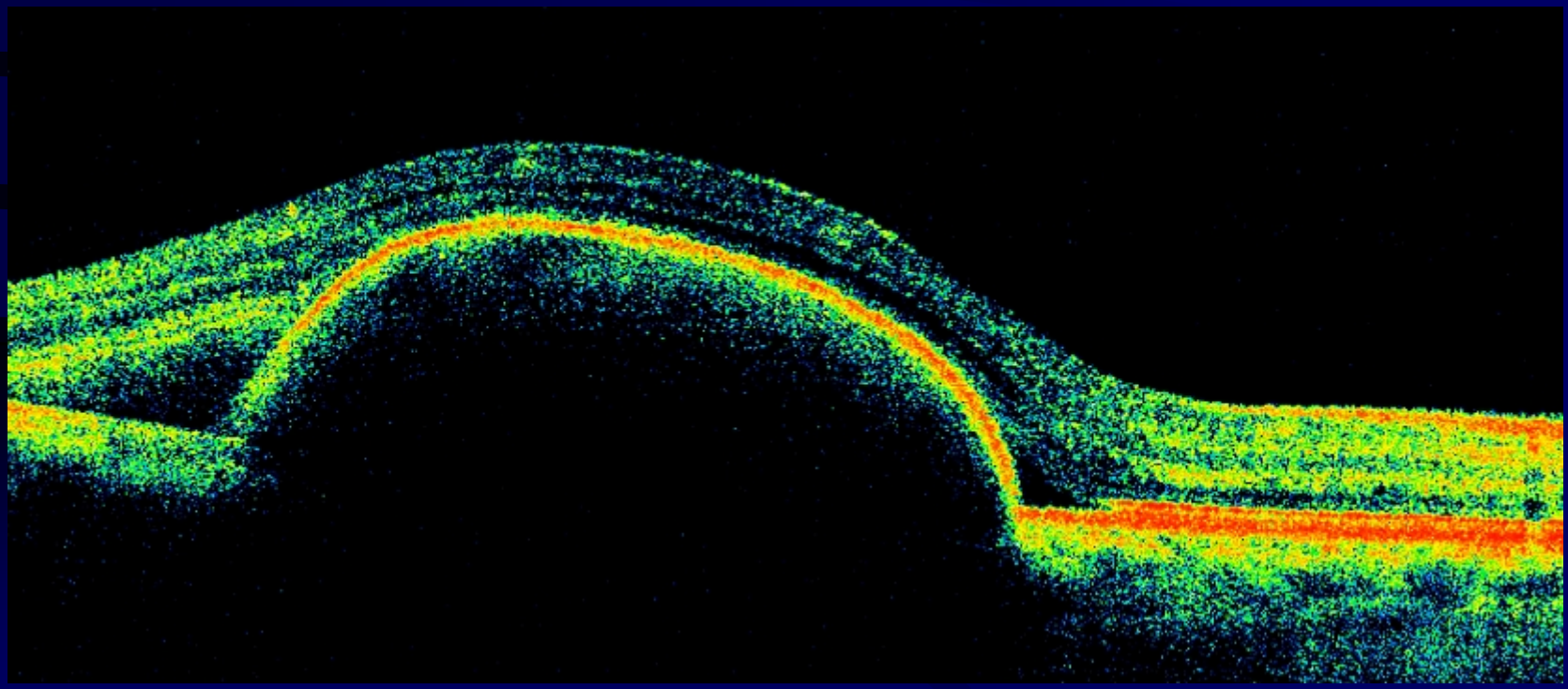


Response to anti-VEGF

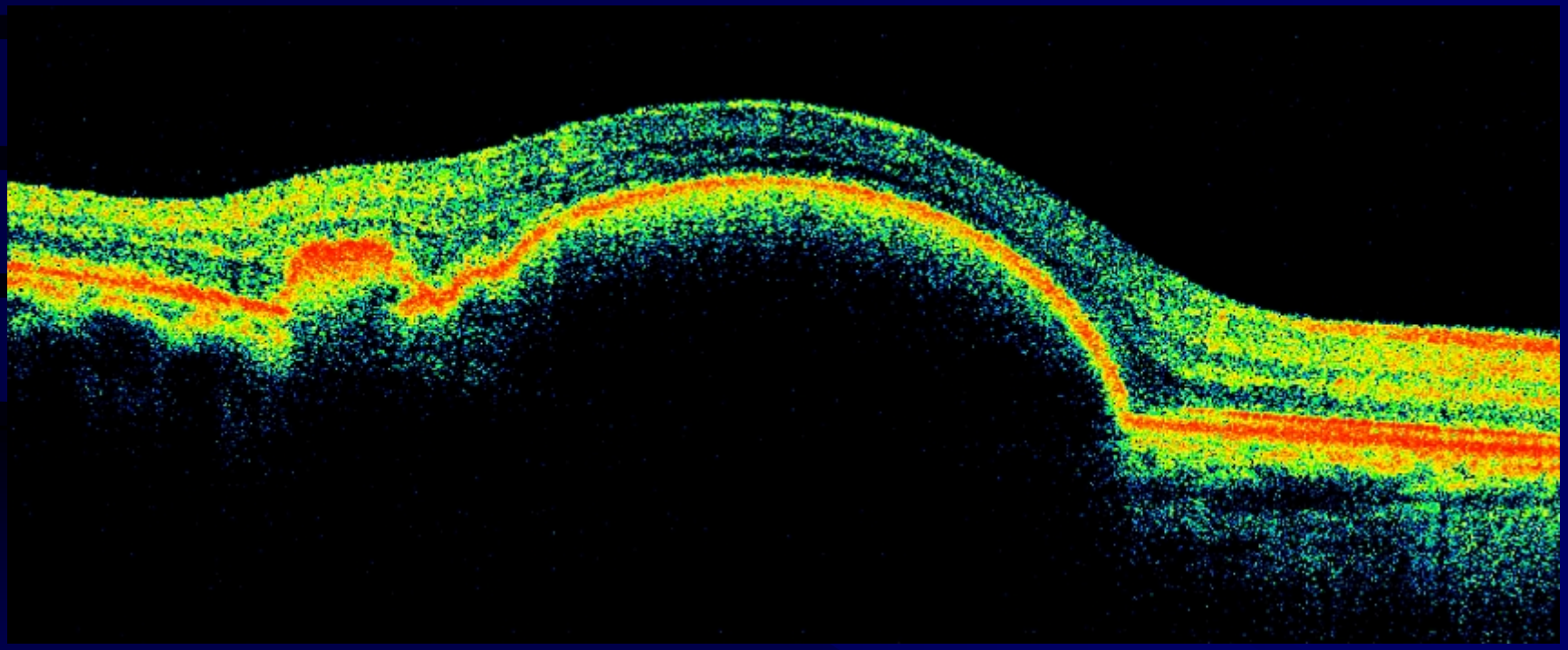



Haemorrhagic leson wet AMD

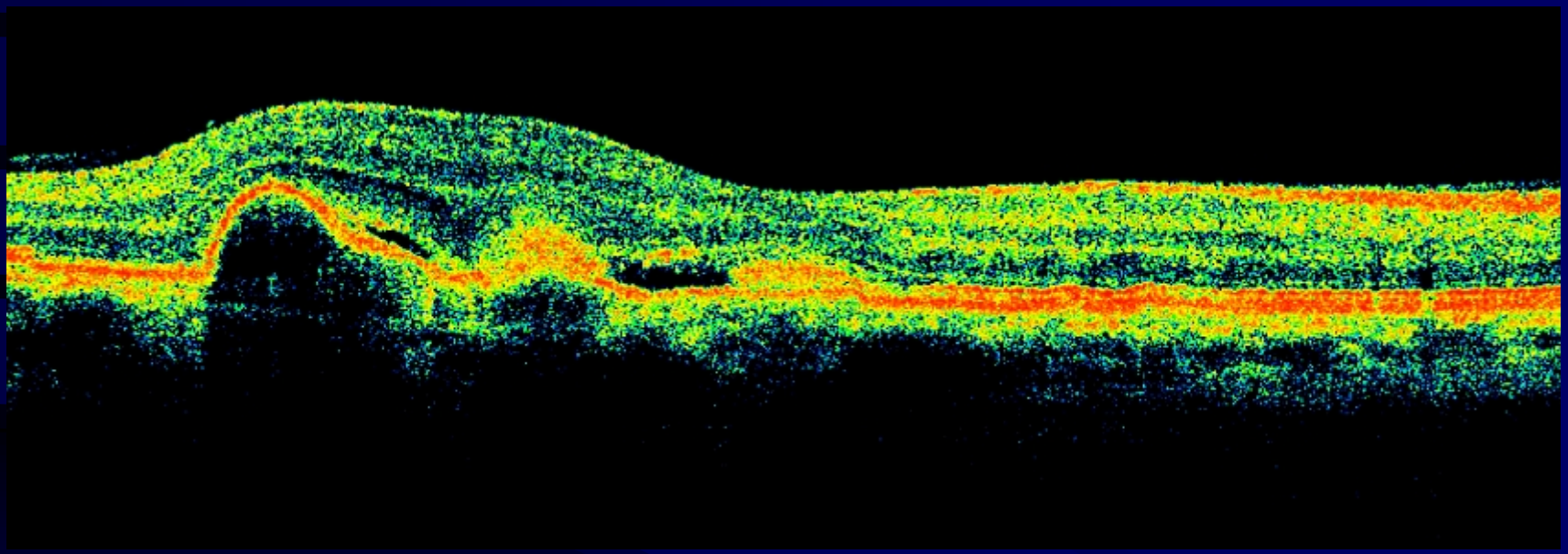
- Massive RPED
- Sensory retinal detachment
- All outer retinal layers compressed over lesion



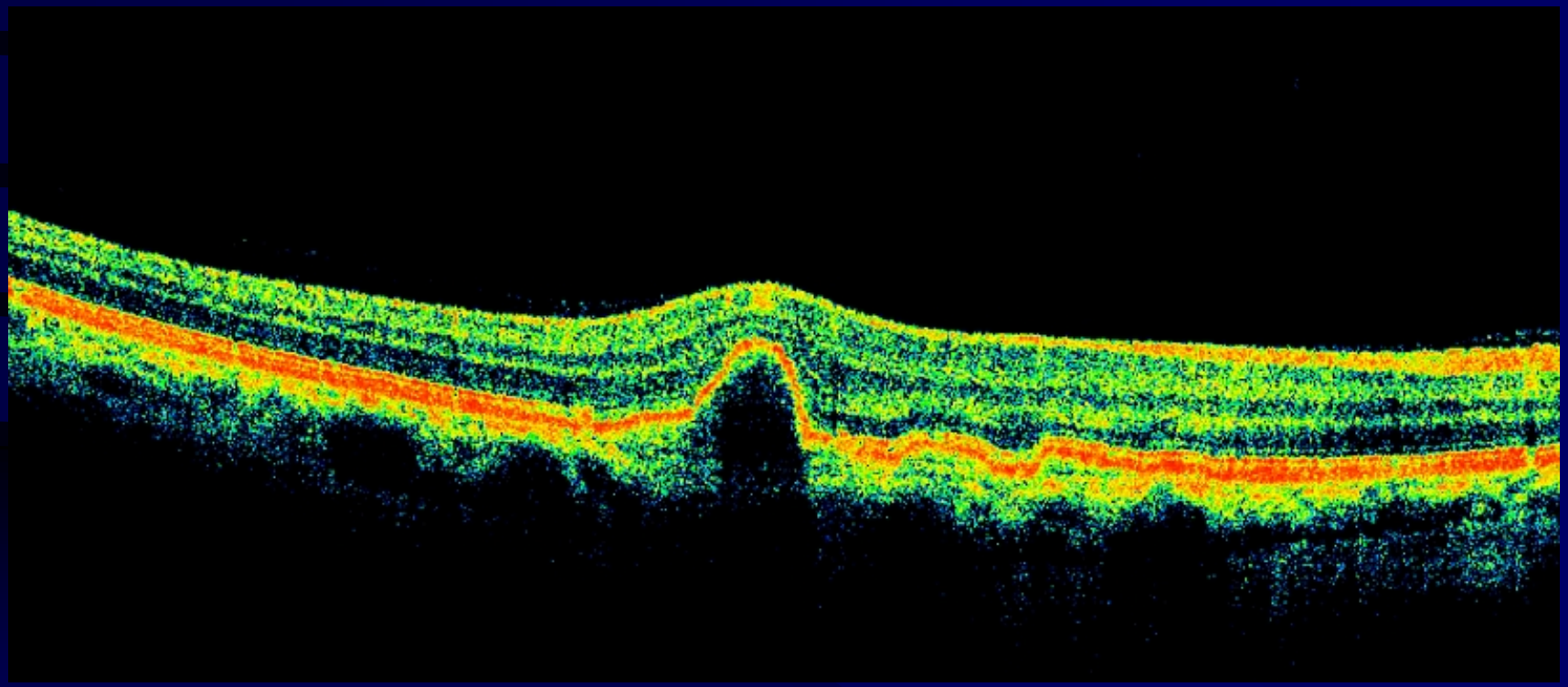
2 weeks post anti-VEGF



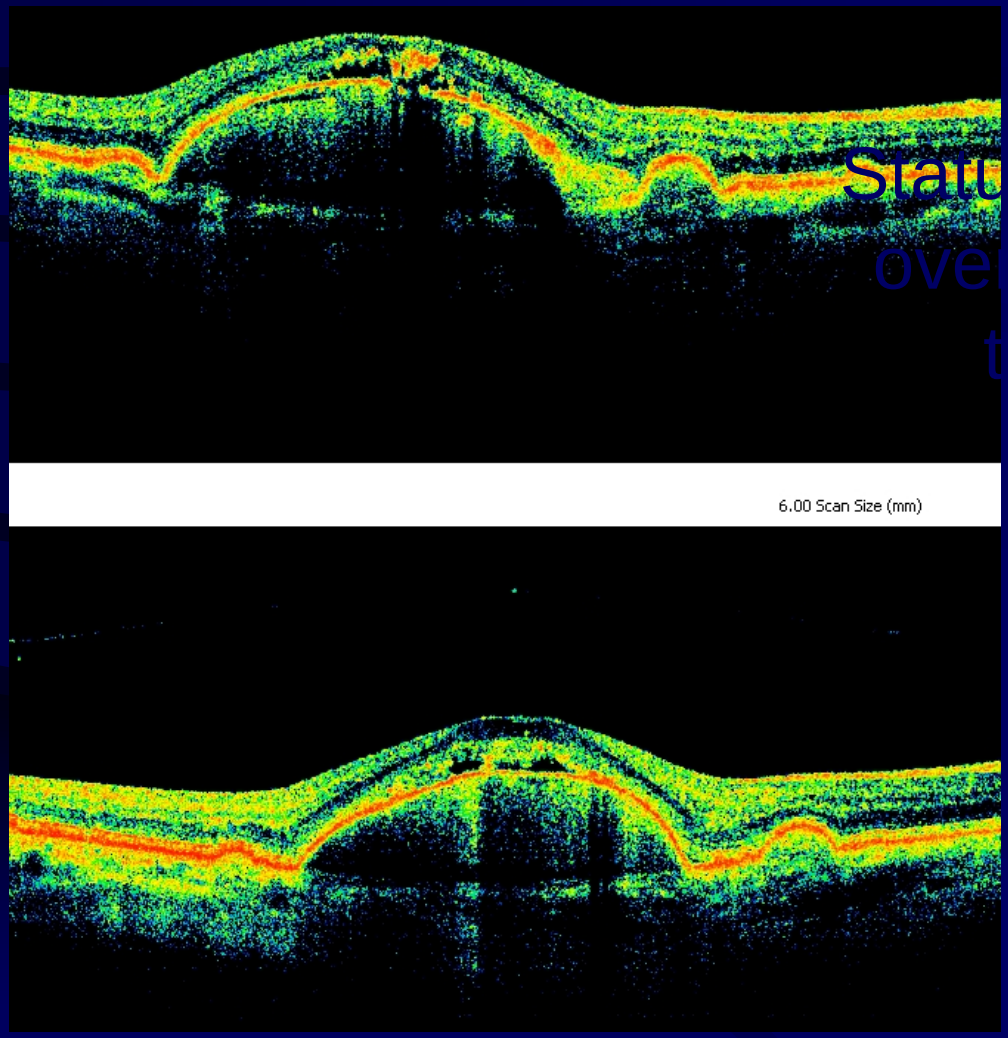
4 weeks post anti-VEGF



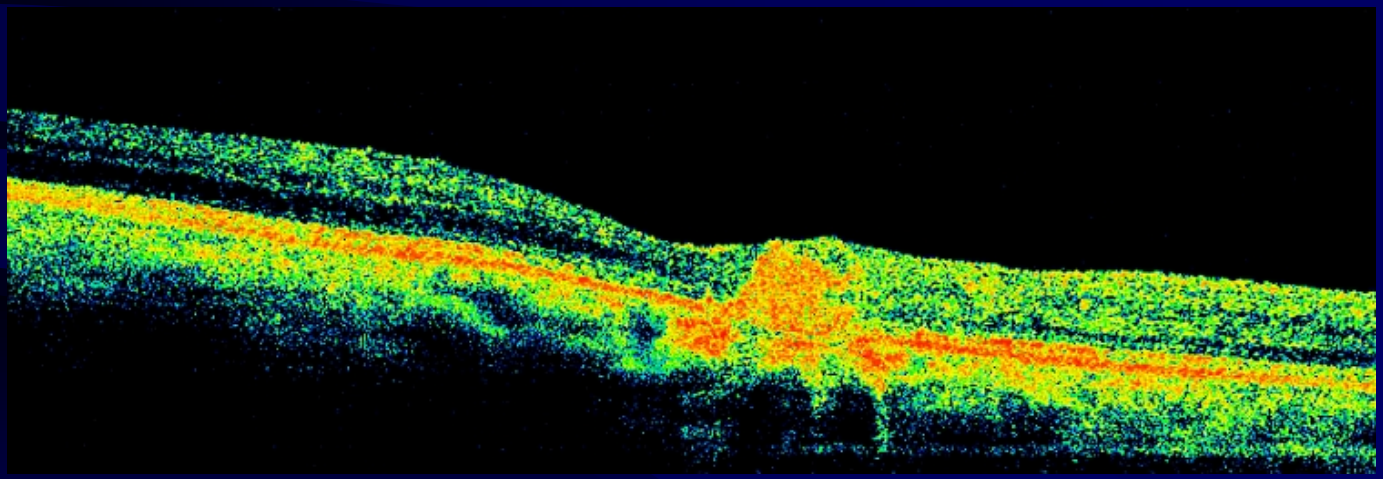
12 weeks after starting anti-VEGF



CNVM with RPED
Stable without therapy over 4 years



- Clump of Neovascularisation
- RPE irregularity
- No fluid: no activity, can observe



Bevacizumab versus Ranibizumab
The Verdict

Complications of AMD Treatment Trial

CATT

CATT Methods

- Multicenter, single-blind, noninferiority trial
- 1208 patients assigned randomly to ranibizumab or bevacizumab
- Either monthly schedule or as-needed with monthly evaluation
- Primary outcome: mean change in VA at 1 year

CATT Results

- Bevacizumab monthly was equivalent to ranibizumab monthly, with 8.0 and 8.5 letters gained, respectively
- Bevacizumab as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained respectively

CATT Results

- Ranibizumab as needed was equivalent to monthly ranibizumab
- Comparison between bevacizumab as needed and monthly bevacizumab was inconclusive
- Mean decrease in retinal thickness was greater in the ranibizumab-monthly group than in the other groups (196 μm vs 160 μm)

CATT Results
Adverse events

- Rates of death, MI, stroke similar for both
- Serious systemic adverse events/ hospitalizations higher with bevacizumab (24.1% vs. 19.0%; risk ratio, 1.29)
- Disease categories not identified as areas of concern

CATT Conclusions

- At 1 year, both drugs had equivalent effects on VA
- Ranibizumab given as needed with monthly evaluation had effects equivalent to monthly ranibizumab
- Differences in rates of serious adverse events require further study

CATT Conclusions

- Results support the use of either bevacizumab or ranibizumab for AMD
- As-needed regimen is an acceptable alternative to monthly regimen, but strict compliance on review is required
- Health care providers will need to justify the cost of using ranibizumab

CATT Conclusions

- CATT data support the continued global use of intravitreal bevacizumab as an effective, low-cost alternative to ranibizumab

Avastin & Lucentis
Current status

Avoid with recent TIAs / history of stroke / cardiovascular disease specially in the last 1 month

Directions for the Future

- How many injections ?
- VEGF Trap 2 monthly…
- Ideal long-acting form far from view

Thank You!