Update On AMD

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UPDATES ON AMD

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What is new...

- In diagnostic
- In therapeutic

… prognostic

Diagnostic

- Autofluorescence imaging
- High resolution OCT
- Combined OCT, SLO and mfERG
- Macular perimetry (+mfERG)
- ….

  - When to do, indication(s)

ANTI-ANGIOGENESIS in EYE

The man who doesn't know the history, they don't have future

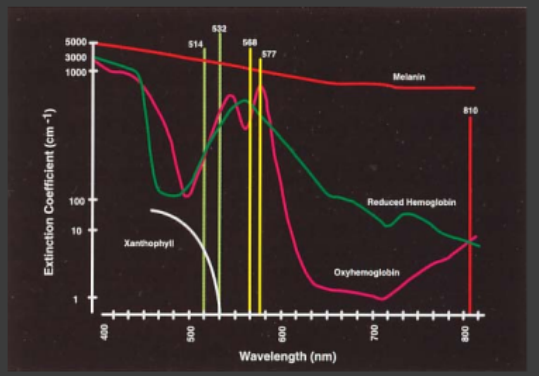
Extrapolate from cancer treatment (NV)

14 Folkman, J. Tumor angiogenesis: therapeutic implications. Science 1971,18:1182-6

5 Miller et al. VEGF is temporally and spatially correlated with ocular angiogenesis in a primate model. Am J Pathol 1994; 145: 574–584.

The Past AND Present

- NON-PHARMACOTHERAPY:
  - MPS, and its role currently(foveolar, juxtafoveolar, extrafoveolar, paramacular, extramacular, etc). Recurrency 54% at long term
  - SST, and its role currently (type 1 & 2)



- PHARMACOTHERAPY COMBINATION (10 yrs)
  - PDT (photosensitizer)/TTT (w/wo photosensitizer), alone/combined
    - Predominantly classic, minimally classic, occult CNV. Rather preserving than improving VA

The Past (ctd.)

- PHARMACOTHERAPY:
  - Pegabtanib, FDA Dec 2004, 6 wks interval IV, rather preserving than improving VA
  - July 2005, Systemic Avastin for the Treatment of Neovascular AMD (SANA) trial as well as case reports of intravitreal bevacizumab use supported by optical coherence tomography (OCT) documentation.
  - …

Commencing the Anti-VEGF era

Anti-VEGF Trial

- Year 2006 (bevacizumab available 2005, used with multiple uncontrolled studies. No obvious evidence of side effects or safety issues, OFF LABEL use)
  - Marina study : a placebo-controlled trial of ranibizumab
  - Anchor study : a randomized comparison of ranibizumab and photodynamic therapy
- Ranibizumab approved June 2006

Trial (ctd.)

- Medicare Part B (2008)
  - bevacizumab accounted for 58%, ranibizumab for 41%, and macugen 1%

    Am J Ophthalmol 2011;151:887-95.
  - Indonesia (?)
- PRONTO study
- PIER study
  - Rani- dosing, 1 year result etc

6 years of OFF LABEL use of avastin in US (2011)

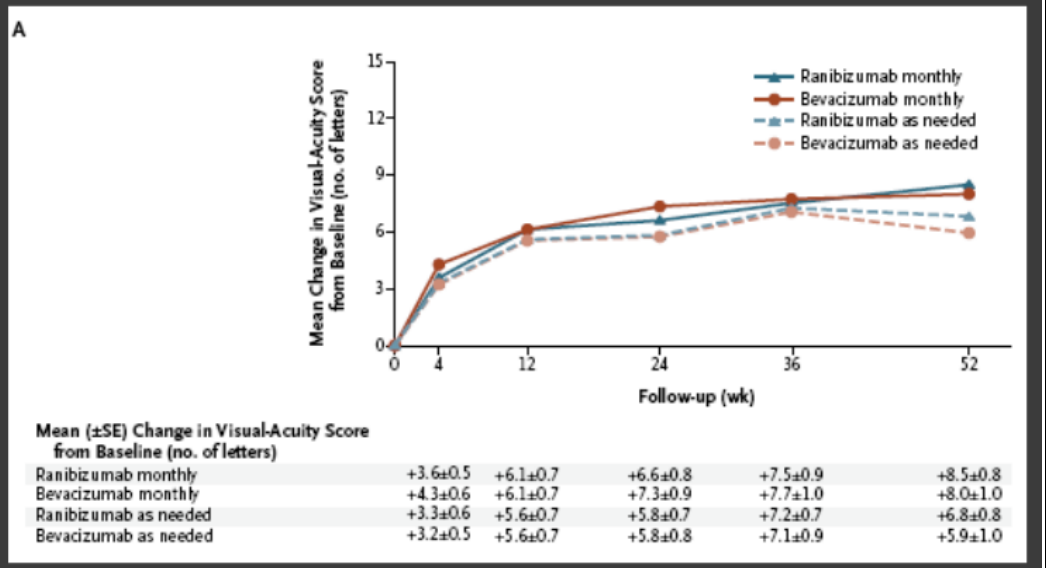
Other issues

Government Driven Research

- Bevacizumab *vs* Ranibizumab, non-inferiority trial
  - CATT study : NIH, US
    - Primary outcome : there were equivalent mean changes in visual acuity averaged over the 1-year period
    - noninferiority limit of 5 letters on the eye chart
  - IVAN study : UK
    - Noninferiority limit was 3.5 letters

CATT study 1 year (beva- *vs* rani-)

- Administered monthly : equivalent (VA 8.0 vs 8.5 gained)
- Administered as needed : equivalent (5.9 vs 6.8 gained)[3]
- Rani- monthly *vs* as needed : equivalent
- Beva- monthly *vs* as needed : inconclusive

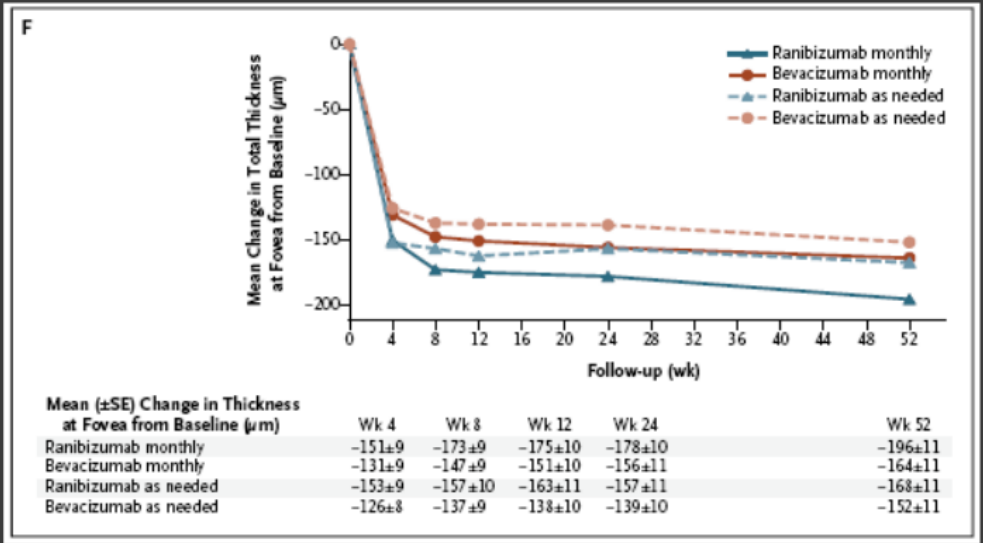


Mean (±SE) Change in Visual-Acuity Score from Baseline (no. of letters)					
Ranibizumab monthly	+3.6±0.5	+6.1±0.7	+6.6±0.8	+7.5±0.9	+8.5±0.8
Bevacizumab monthly	+4.3±0.6	+6.1±0.7	+7.3±0.9	+7.7±1.0	+8.0±1.0
Ranibizumab as needed	+3.3±0.6	+5.6±0.7	+5.8±0.7	+7.2±0.7	+6.8±0.8
Bevacizumab as needed	+3.2±0.5	+5.6±0.7	+5.8±0.8	+7.1±0.9	+5.9±1.0

CATT Study.[12] N Engl J Med 2011;364:1897-908

CATT study 1 year (ctd.)

- mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 µm) than in the other groups (152 to 168 µm, P = 0.03 ANOVA)



Mean (±SE) Change in Thickness at Fovea from Baseline (µm)	Wk 4	Wk 8	Wk 12	Wk 24	Wk 52
Ranibizumab monthly	−151±9	−173±9	−175±10	−178±10	−196±11
Bevacizumab monthly	−131±9	−147±9	−151±10	−156±11	−164±11
Ranibizumab as needed	−153±9	−157±10	−163±11	−157±11	−168±11
Bevacizumab as needed	−126±8	−137±9	−138±10	−139±10	−152±11

Patients concern *vs* doctors concern

CATT study 1 year (ctd.)

- [3] Rates of death, myocardial infarction, and stroke were similar (P>0.20)
- [9] Serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab.

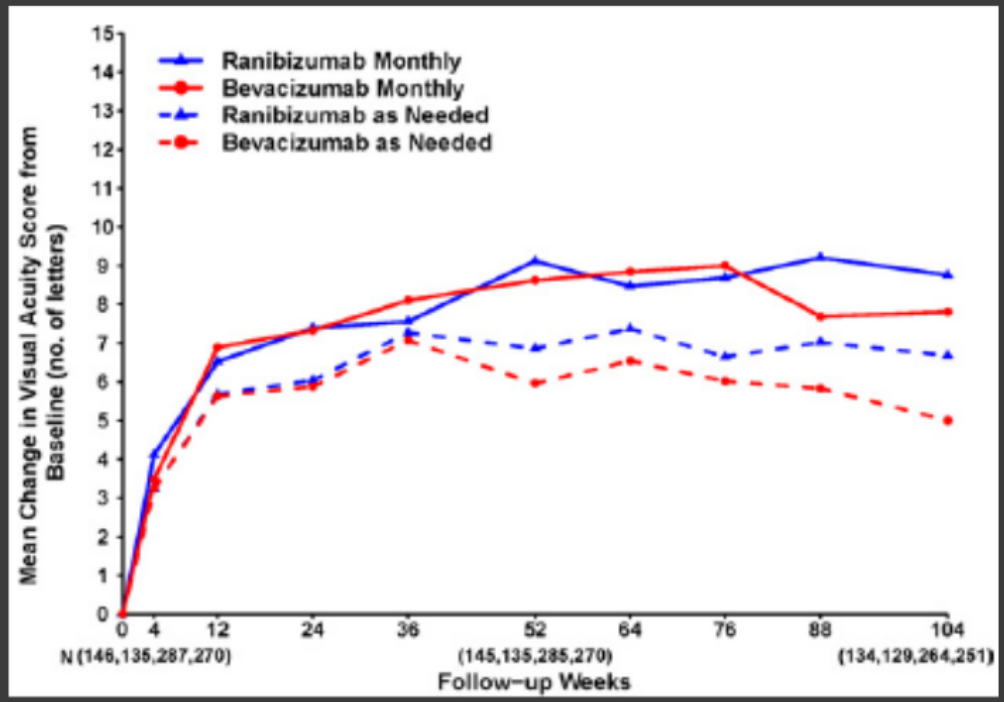
  Needs cautious interpretation
- Average cost of drug/patient ($) —
  - Monthly rani- 23,400 39x
  - Monthly beva- 595
  - As needed rani- 13,800
  - As needed beva- 385

CATT study 2 year

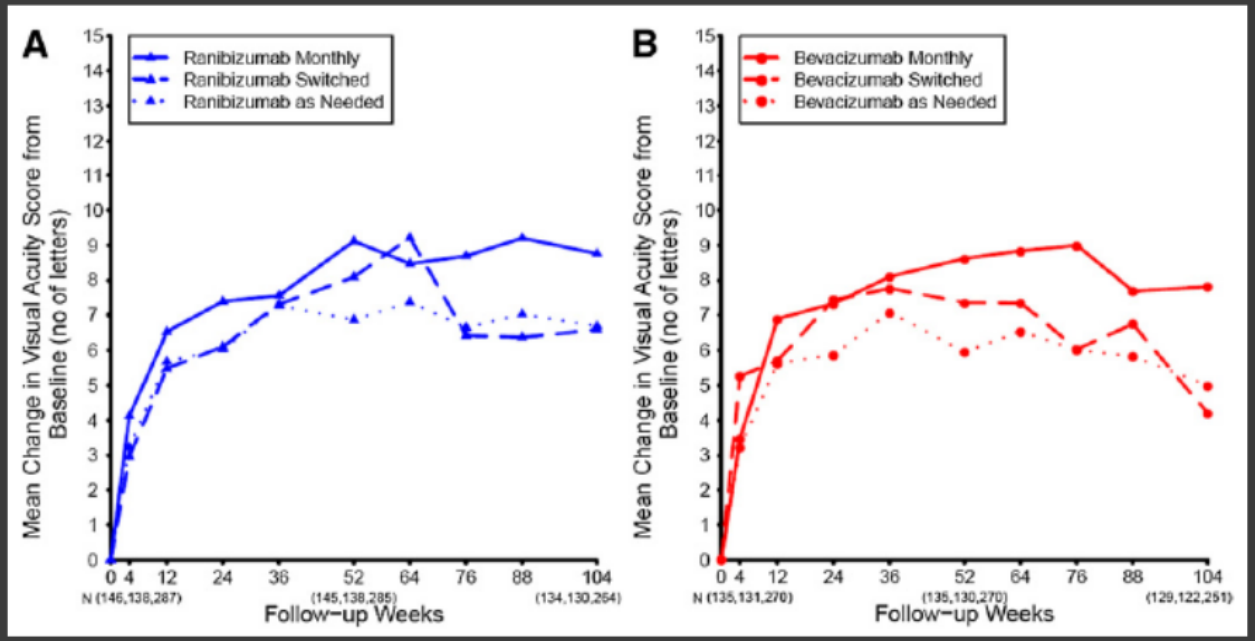
- To describe effects of ranibizumab and bevacizumab when administered monthly or as needed for 2 years (longer effects)
- To describe the impact of switching to as-needed treatment after 1 year of monthly treatment.
- As previous design (4 treatment arms).
  - At 1 year, patients initially assigned to monthly treatment were reassigned randomly to monthly or as-needed treatment, without changing the drug assignment
- **Main Outcome Measures:** Mean change in VA

CATT Research Group. Ophthalmology 2012

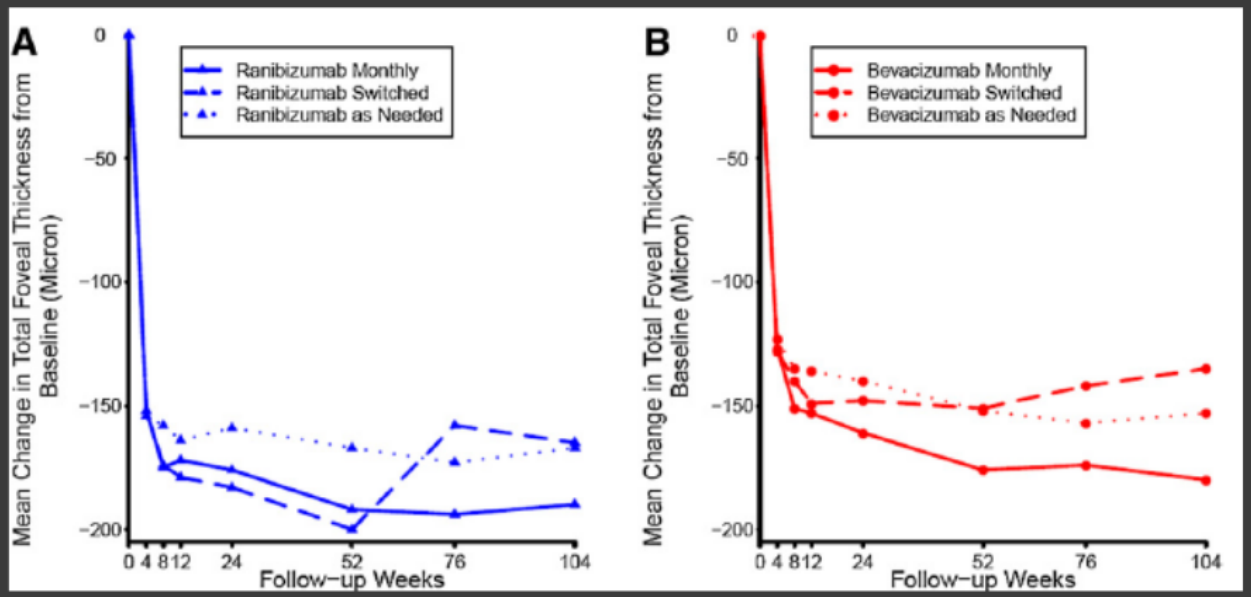
- For 2 years, mean gain in visual acuity was similar, P=0.21[3]
- administered as needed : equivalent (5.9 vs 6.8 gained)
- Rani- monthly *vs* as needed : equivalent
- Beva- Administered monthly *vs* as needed : inconclusive



- Mean gain was greater for monthly than for as-needed treatment
- Switching from monthly to as-needed treatment resulted in greater mean decrease in vision during year 2 (2.2 letters; *P 0.03) and a* lower proportion without fluid (19%; *P 0.0001).*



- The proportion without fluid ranged from 13.9% [3] in the bevacizumab-as-needed group to 45.5% in the ranibizumab monthly group (drug, *P 0.0003; regimen, P 0.0001).*



- Rates of death and arteriothrombotic events were similar
- Proportions of patients with 1 or more systemic serious adverse events was higher with bevacizumab than ranibizumab (39.9% vs. 31.7%; adjusted risk ratio, 1.30; 95% CI, 1.071.57; *P 0.009). (Inconsistent with IVAN Study result)*

Read cautiously, since older patients (>80 years) more in beva- arm than rani- arm

IVAN Study 1 year

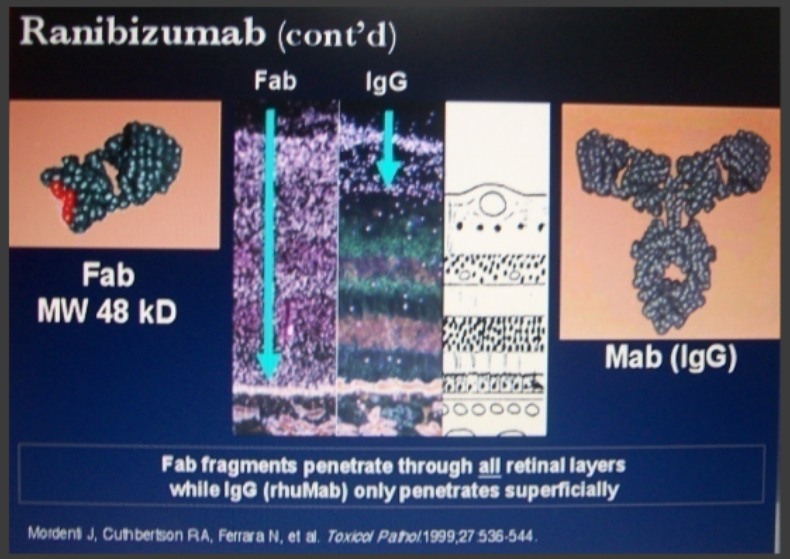
- 4 arm, noninferiority limit was 3.5 letters
- The comparison of visual acuity at 1 year between bevacizumab and ranibizumab was inconclusive.
- Visual acuities with continuous and discontinuous treatment were equivalent.
- Other outcomes are consistent with the drugs and treatment regimens having similar efficacy and safety.

Ophthalmology 2012. Epub ahead 2012 May 11

- Fewer participants receiving bevacizumab had an arteriothrombotic event or heart failure (odds ratio [OR], 0.23; 95% CI, 0.05 to 1.07; *P 0.03).*
- There was no difference between drugs in the proportion experiencing a serious systemic adverse event (OR, 1.35; 95% CI, 0.80 to 2.27; *P 0.25).*
- Serum VEGF was lower with bevacizumab (GMR, 0.47; 95% CI, 0.41 to 0.54; P0.0001) and higher with discontinuous treatment (GMR, 1.23; 95% CI, 1.07 to 1.42; *P 0.004).*

Beva- vs rani- compound, to consider

- Monoclonal antibodi
- Total (149 kDa) vs fractionated (48kDa).
- Fc role, less easy penetration and longer effect *vs* easier penetration through ILM and shorter effect N Engl J Med 2006;355(14):1409 –1412
- The intravitreal half-lives of rani- and beva-, were estimated to be 3.2 and 5.6
  Retina. 2012 Mar;32(3):434-57.



Aflibercept (VTE)

- VEGF trap-eye 2 mg (0.05 ml; EYLEA™) injected either monthly or every other month was comparable to monthly dosing of ranibizumab in visual acuity gain and safety.
- Nov 18 2011, FDA approval for the treatment of patients with neovascular age-related macular degeneration.

  Nat Rev Drug Discov. 2012
- The FDA's Ophthalmic Drug Advisory Committee recommended for monthly inj for 3 months then every 2 months dosing

EYLEA (ctd)

- A 115-kDa recombinant fusion protein consisting of the VEGF-binding domains of human VEGF receptors 1 and 2 fused to the Fc domain of human IgG1 and inhibits all VEGF isoforms and placental growth factor.
- Its high VEGF affinity attributes to the binding sequences from the native receptors VEGFR1 and VEGFR2

Every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept [11]

on selected patients who had a poor response to monthly therapy

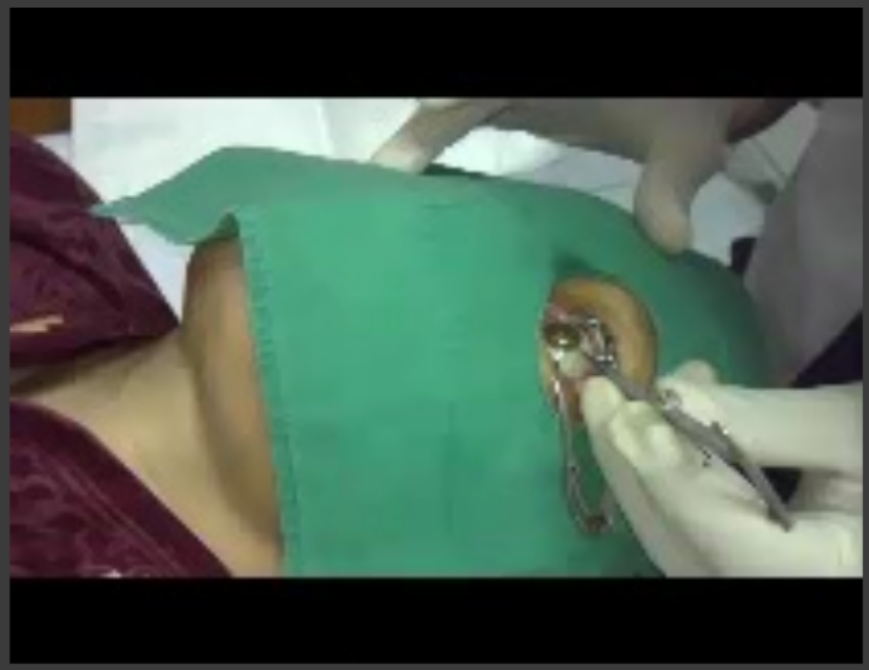
- bevacizumab every 2 weeks has binding levels that were superior to monthly dosing with ranibizumab at a dose of 0.5 mg and potentially superior to the levels achieved when ranibizumab was dosed monthly at a dose of 2.0 mg.
- The VTE displayed superior binding levels for both peak and trough levels even when compared with ranibizumab doses given every 2 weeks.
- half-lives of ranibizumab, bevacizumab, and the VTE were estimated to be 3.2, 5.6, and 4.8 days, respectively

(PS… beva 1 mg monthly ?)

Retina. 2012 Mar;32(3):434-57.

Several considerations …..

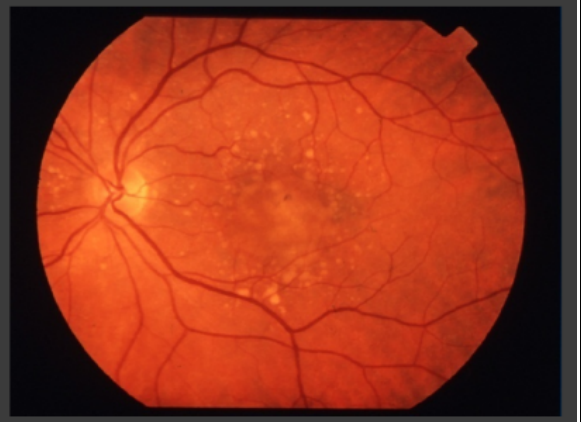
- Patient dyscomfort for 2 years
  - intravitreal inj. for 2 years? Shorter or longer interval
- Combination therapy with steroid ?
  - Longer acting ? PDT and IVTA result

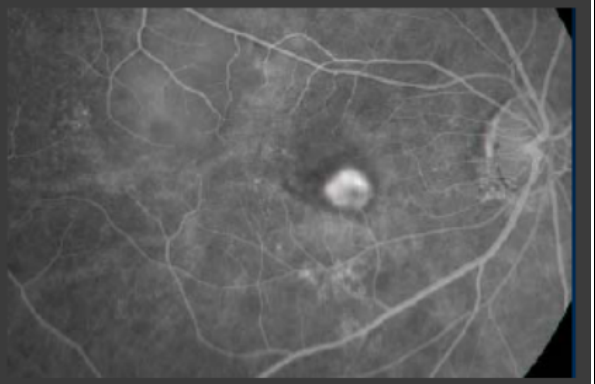


why steroid ?

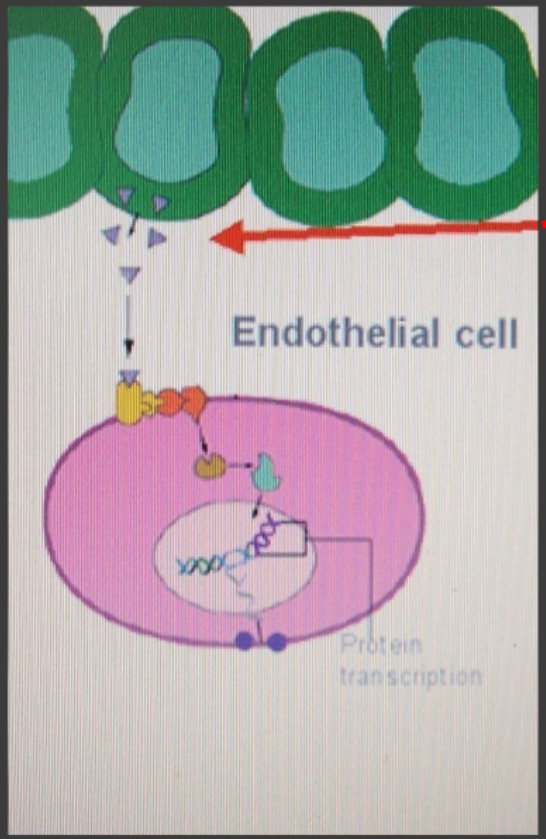
Process of Angiogenesis

- NV : proliferation of new vessels
- Development of new blood vessels from pre-existing, mature vascular network
  - Distinct from vasculogenesis (de novo blood vessel growth in development)
- Follows stochastic series of events, each step dependent upon the previous
  - Inhibition of any step aborts the process





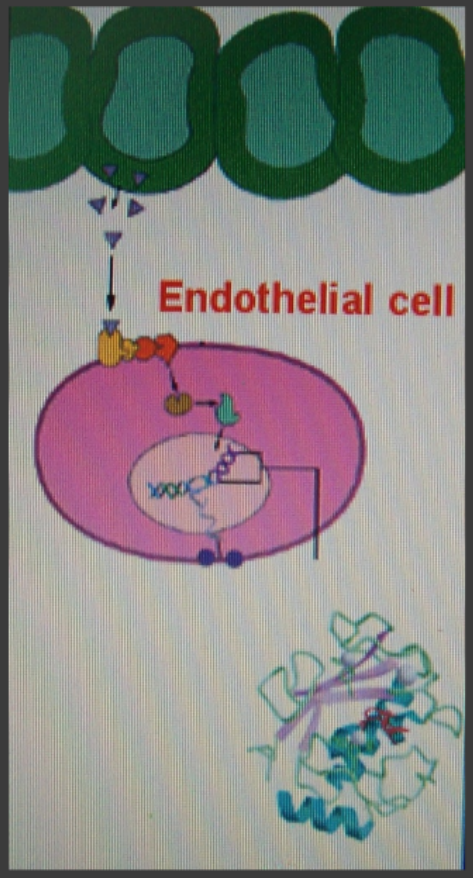
Steps in Neovascularization



1. Angiogenic signal
   - VEGF
   - FGF
   - PEDF
   - Inflammatory cytokines*

* Br J Ophthalmol. 2011 Dec;95(12):1631-7. Epub 2011 May 5.

Steps in Neovascularization



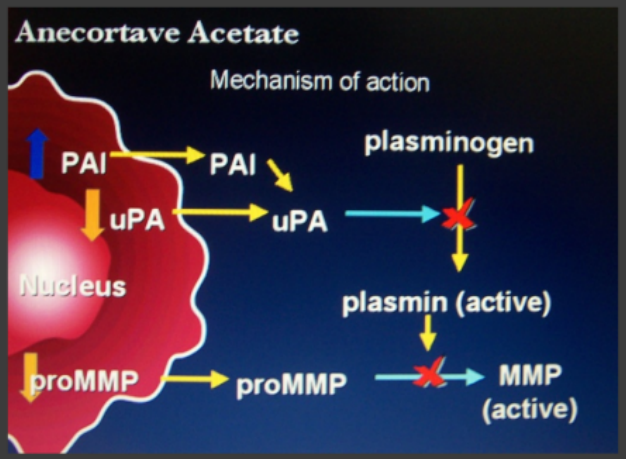
1. Angiogenic signal
2. Endothelial cell activation
3. MMP induction
4. Extracellular matrix remodeling
5. Vascular endothelial cell (VEC) migration
6. VEC proliferation
7. Lumen formation
8. Vascular stabilization

VEGF blockers

- Specific VEGF inhibition
- Antiproliferative-antipermeability effects
- Intravitreal route of administration
- Treatment approaches
  - Monotherapy
  - Combination therapy

Corticosteroid Use for Wet AMD

- Principal effects
  - Stabilizes blood-retinal barrier
  - Resorption of exudation
  - Down regulation of inflammatory stimuli
- Secondary effect
  - Antiangiogenesis



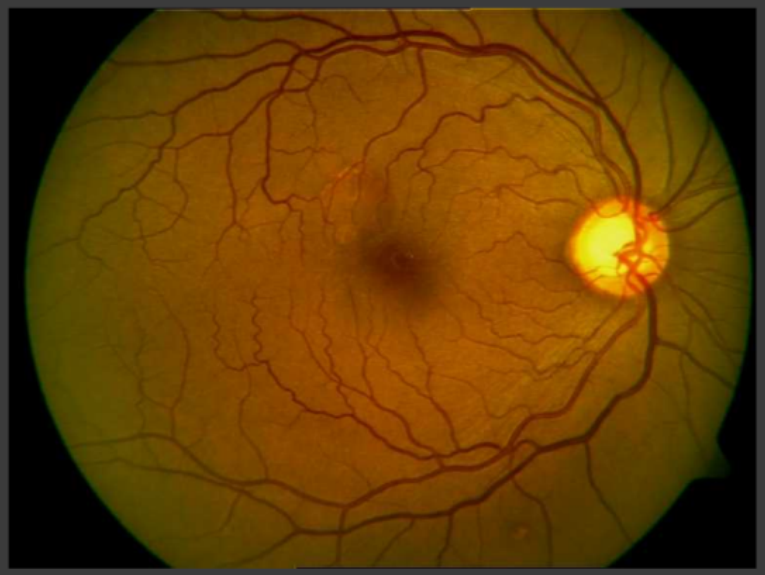
- Intra vitreal injection
  - Triamcinolone acetate (Kenacort™)
  - Duration 4-6 months
- Intra vitreal implants
  - Fluocinolone (Retisert™) : 3 years
  - Dexamethasone (Ozurdex®) : 3-4 months

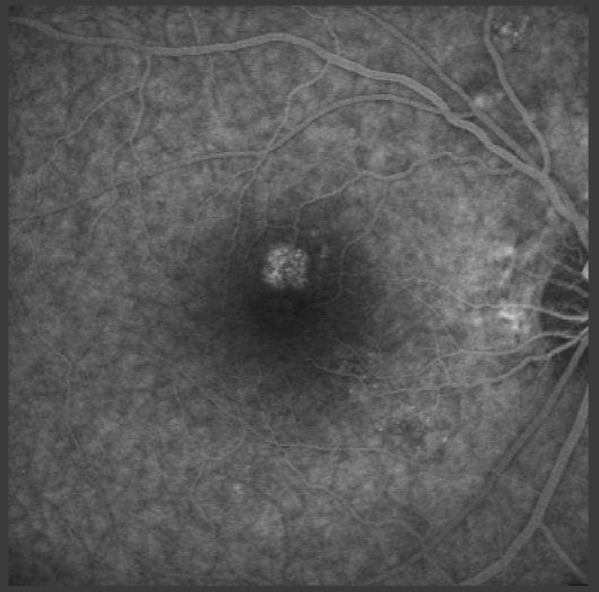
Factors to consider in steroid : limited data available for CNV

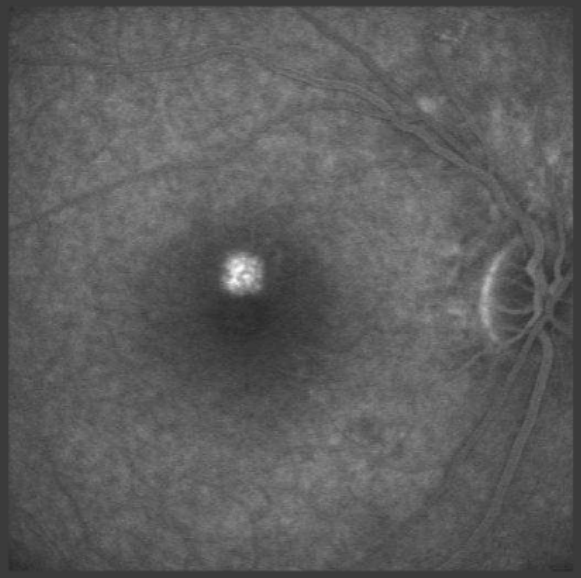
Radio therapy…

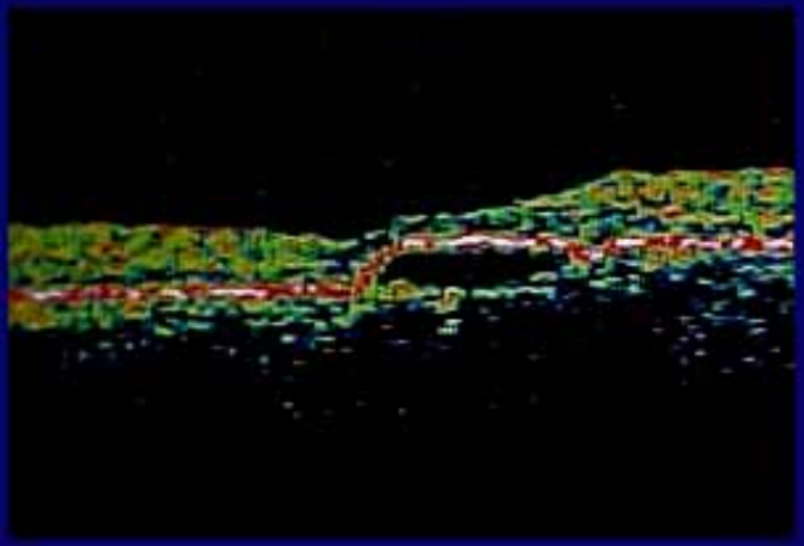
- Logic behind
- Technique and limitations
  - Pre-retinal
  - Sub-retinal/foveal : equal treatment and control in progression. Br J Ophthalmol 2005;89:1045–1051

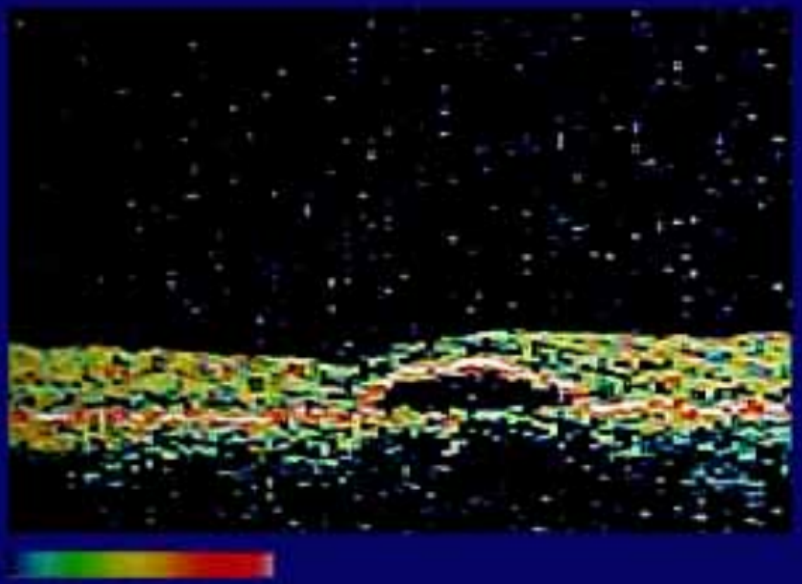
Pigment Epithelial Detachment



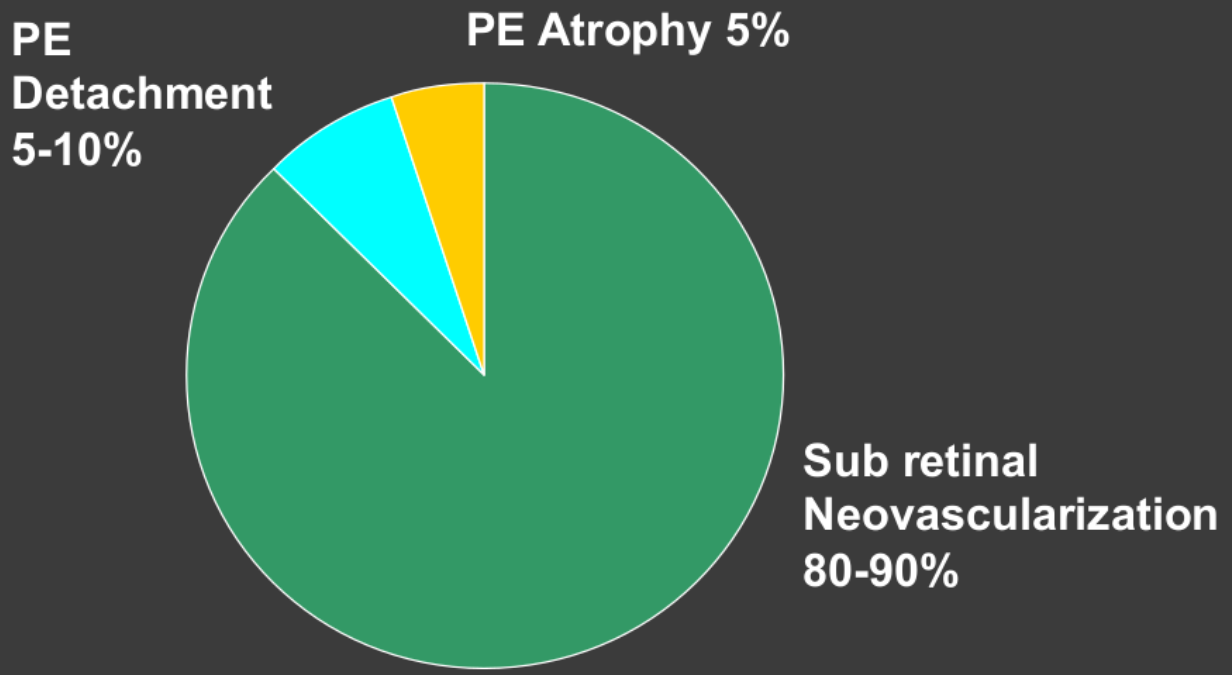








(?) PED Treatment



Reason for vision loss in ARMD

Table 1. Physiologic processes involving VEGF [adapted from ref. 13]

Alveolar septal cell survival
Bone growth and fracture healing
Cardiac development
Dendritic cell differentiation and function
Endothelial cell proliferation, survival and recruitment
Female reproductive function
Glomerulogenesis and kidney function
Induction of plasminogen activator, endothelial nitric oxide and matrix metalloproteinases
Lung maturation
Maintenance of the microvasculature in many organs
Monocyte/macrophage chemoattraction
Neovascularization following myocardial infarction and stroke
Neural cell survival
Pancreatic islet cell survival
Protection of hepatic cells from toxic damage
Skeletal muscle regeneration
Trophic support of choriocapillaris
Vasodilation
Vascular permeability
Wound healing

Ophthalmologica 2012;227(suppl 1):2–10

mauliate

(THANK YOU)

Update On AMD

ORIGINALITY REPORT

19%	11%	16%	11%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Mark S. Blumenkranz, Loh-Shan Leung, Daniel F. Martin, Philip J. Rosenfeld, Marco A. Zarbin. "Pharmacotherapy of Age-Related Macular Degeneration", Elsevier BV, 2013 Publication	4%
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9	Samaneh Davoudi, Ramak Roohipourmoallai, Cynthia M. Guerin, Siva S.R. Iyer. "Exacerbation of pigment epithelial detachment following aflibercept: A case of bevacizumab rescue", American Journal of Ophthalmology Case Reports, 2021 Publication	1%
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