Complications and Safety of anti-VEGF Therapy

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Financial Disclosure

- I have no financial interests or relationships to disclose.

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Anti-VEGF Therapy

- Choroidal Neovascularization
  - AMD
  - Myopic
- Diabetic Retinopathy
- Venous Occlusive Disease
- Corneal Diseases

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Anti-VEGF Therapy

- Highly effective treatment for CNV
  - Potentially blinding condition
    (80% of AMD-induced severe visual loss)
  - Previously untreatable, or with still high frequency of failure or recurrence (PDT)
- Complications
  - Systemic
  - Ocular

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Anti-VEGF Therapy

Systemic Complications

- Systemically safe

(Apte RS, Ophthalmology, 2007 Sep)

- Multivariate analysis of available studies could not conclude or rule out possible increased risk of stroke in 0.5 mg group

(AAO Retina 2008 Subspecialty Day)

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Anti-VEGF Therapy

Systemic Complications

1. Bevacizumab (Avastin)
   - PACORES study.
     4303 IVI, 1310 eyes (1173 pts),
     12 months FUP (Grafes Arch Clin Nexp Ophthalmol, 2008 Jan)
   - Systemic adverse effects: 1.5%
     - Systemic blood pressure elevation: 0.59%
     - Cerebrovascular accidents: 0.5%

Anti-VEGF Therapy

Systemic Complications

2. Ranimizumab (Lucentis)

- MARINA study (as well as ANCHOR) did not exclude pts with previous cardiovascular events
- Difference in rate of thromboembolic events: not statistically significant
- ANCHOR (vs. PDT): difference in rate of thromboembolic events: not statistically significant
- SAILOR (**S**afety **A**ssessment **o**f **I**ntravitreal **L**ucentis f**O**R **AMD**) study
  - Interim analysis
  - Higher stroke rate in 0.5 mg dose group
- Data limited to 2-yrs experience in clinical trials, limited number of patients, retrospective studies

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Anti-VEGF Therapy

Ocular Complications

- Endophthalmitis
- Retinal Pigment Epithelium Tears
- Retinal Detachment
- Other

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Anti-VEGF Therapy

Endophthalmitis

- High number of anti-VEGF treatment cases
- Repeated injections per case
- VISION (Macugen) 12/892
  - 1.34%, rate per injection 0.16%
- ANCHOR (Lucentis)
  - 0.72%
- MARINA (Lucentis) 5/477
  - 1.04%, rate per injection 0.05%

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Anti-VEGF Therapy

Endophthalmitis

- 1/5,233 injections (bevacizumab)
  (Mason JO 3rd, Retina, 2008 Apr)
  - 0.00019 % rate per injection
- 1/1,218 injections (684 eyes)(bevacizumab)
  (Jonas JB, J Ocul Pharmacol Ther 2007, Jun)
  - 0.0016%, 0.00082% rate per injection
- 3/10,254 injections (bevacizumab (1/3,501), ranimizumab (2/6,347) pegaptanib (0/406))
  (Pilli S, Am J Ophthalmol, 2008 May)
  - 0.00029% rate per injection

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Anti-VEGF Therapy

Endophthalmitis

- Possible direct inoculation of ocular surface flora (i.e. coag. neg. Staphylococcus) into the vitreous cavity by the injection needle

  (de Caro JJ, Retina, 2008 Jun)

- Little scientifically supported evidence to support most behaviours
- Current strategies generally not evidence based

  (Aiello LP, Retina, 2004 Oct

  Prenner J, AAO Subspecialty Day, Retina, 2007)

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Anti-VEGF Therapy

Endophthalmitis

- Even if exceptionally rare, the severity of endophthalmitis mandates:
  - Careful respect of asepsis
  - If possible, sterile environment (OR)
  - Standardized procedures
  - Attention to postoperative treatment

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Anti-VEGF Therapy

Retinal Pigment Epithelial Tears

- Advanced age
- Setting of vascularized PED in AMD
  - Fibrovascular PED or CNV with PED
- Tear within 4-8 wks from 1st-2nd injection

(Chang LK, Retina, 2007 Jun)

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Anti-VEGF Therapy

Retinal Pigment Epithelial Tears

- Pegaptanib
  (Dhalla MS, Am J Ophthalmol, 2006 Apr)
  (Chang LK, Retina, 2007 Sep)
- Ranibizumab (Bakri SJ, Am J Ophthalmol, 2007 Mar)
- Bevacizumab:
  - 1.6% (Garg S, Clin Experiment Ophthalmol, 2008 Apr)
    93% with occult subfoveal NVM
  - 7.5% (Arias L, Eur J Ophthalmol, 2007 Nov-Dic)
  - 2.9% of all AMD, 7% of AMD with RPE detachment
    (Wong LJ, Retina, 2008 Oct)

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Anti-VEGF Therapy

Retinal Pigment Epithelial Tears

- The conclusion to generally exclude patients with PED from anti-VEGF therapy is not justifiable due to the therapeutic efficiency and associated gain of vision

  (Kook D, Ophthalmologe, 2008 Feb)

- Maintenance of therapy may help preserve vision after RPE tear development

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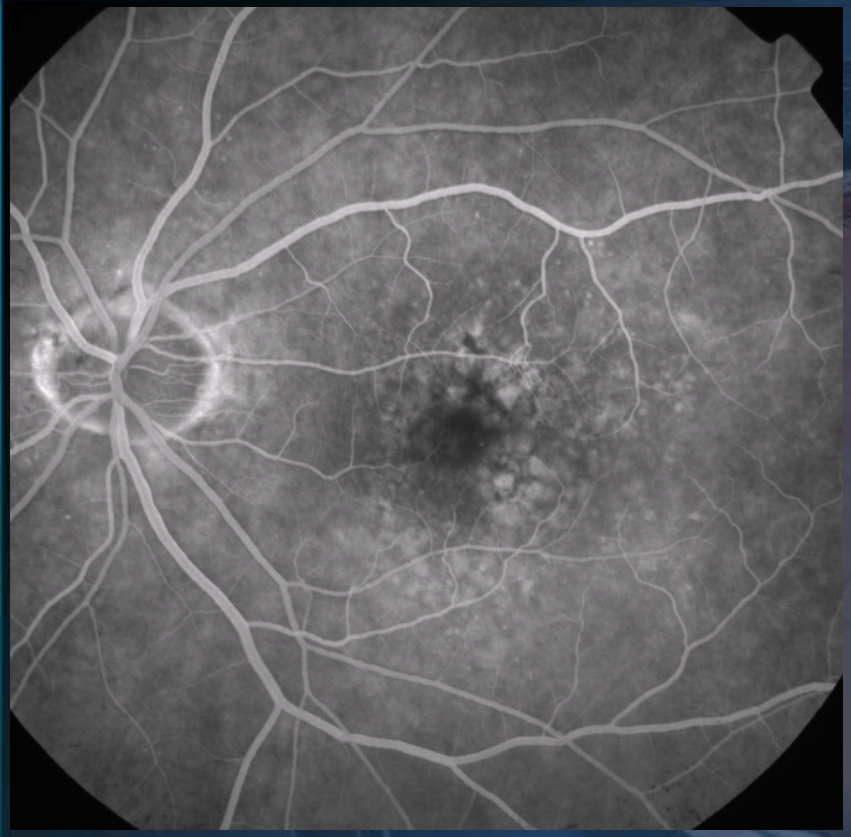
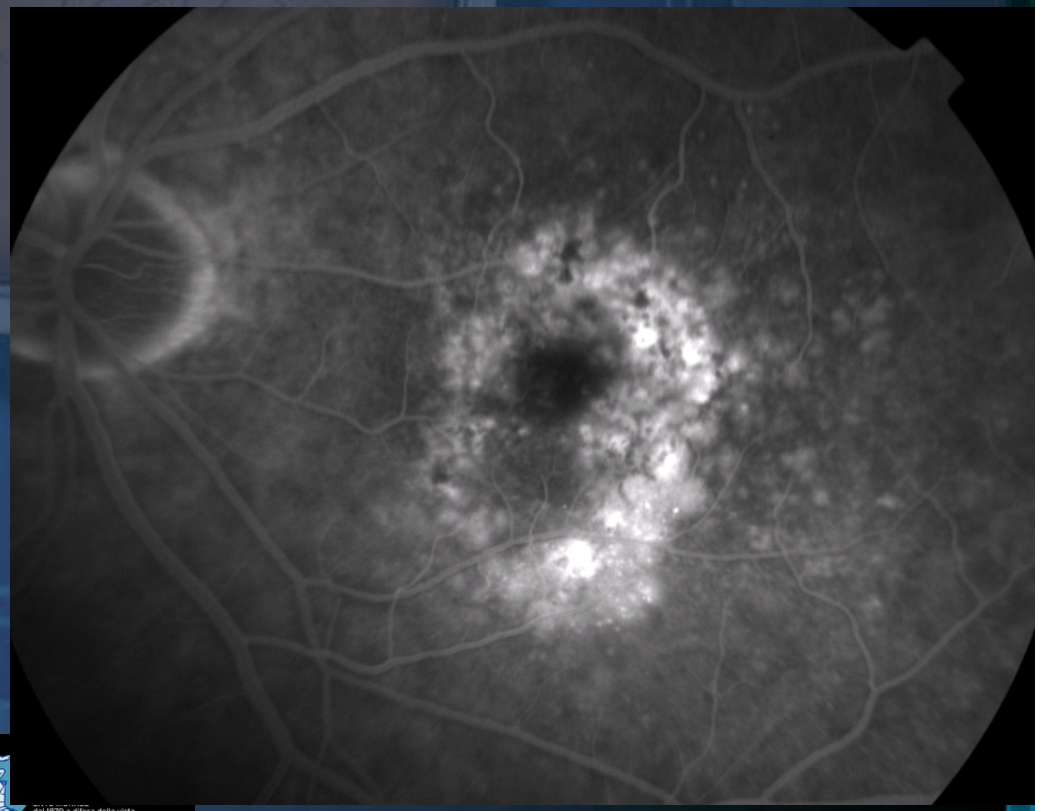
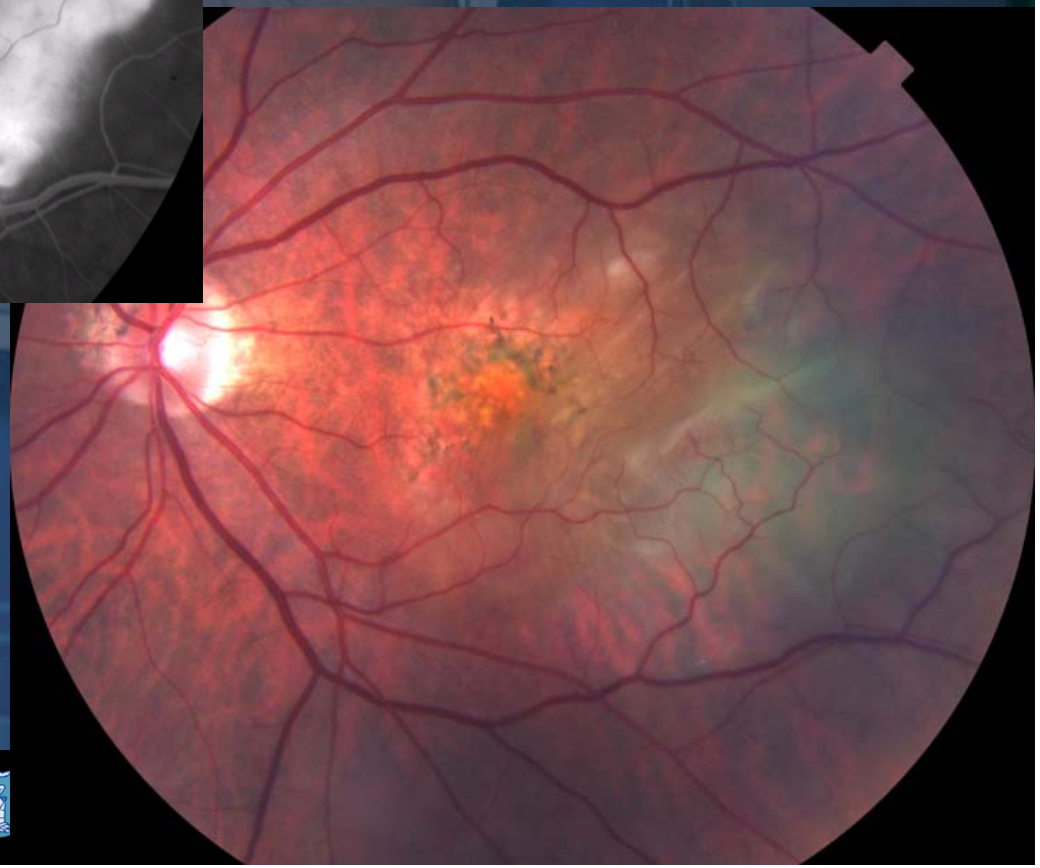
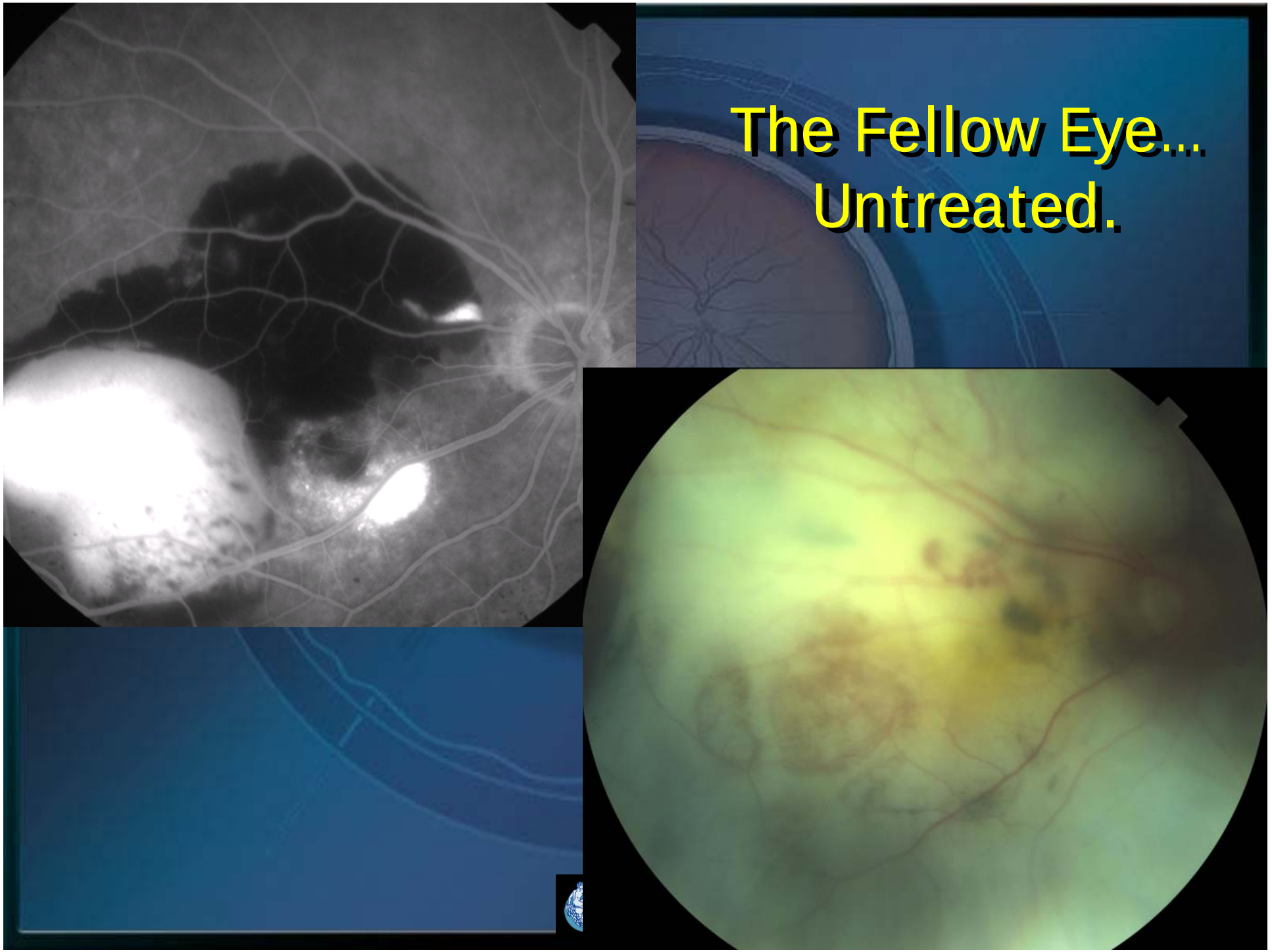
Retinal Pigment Epithelial Tears...



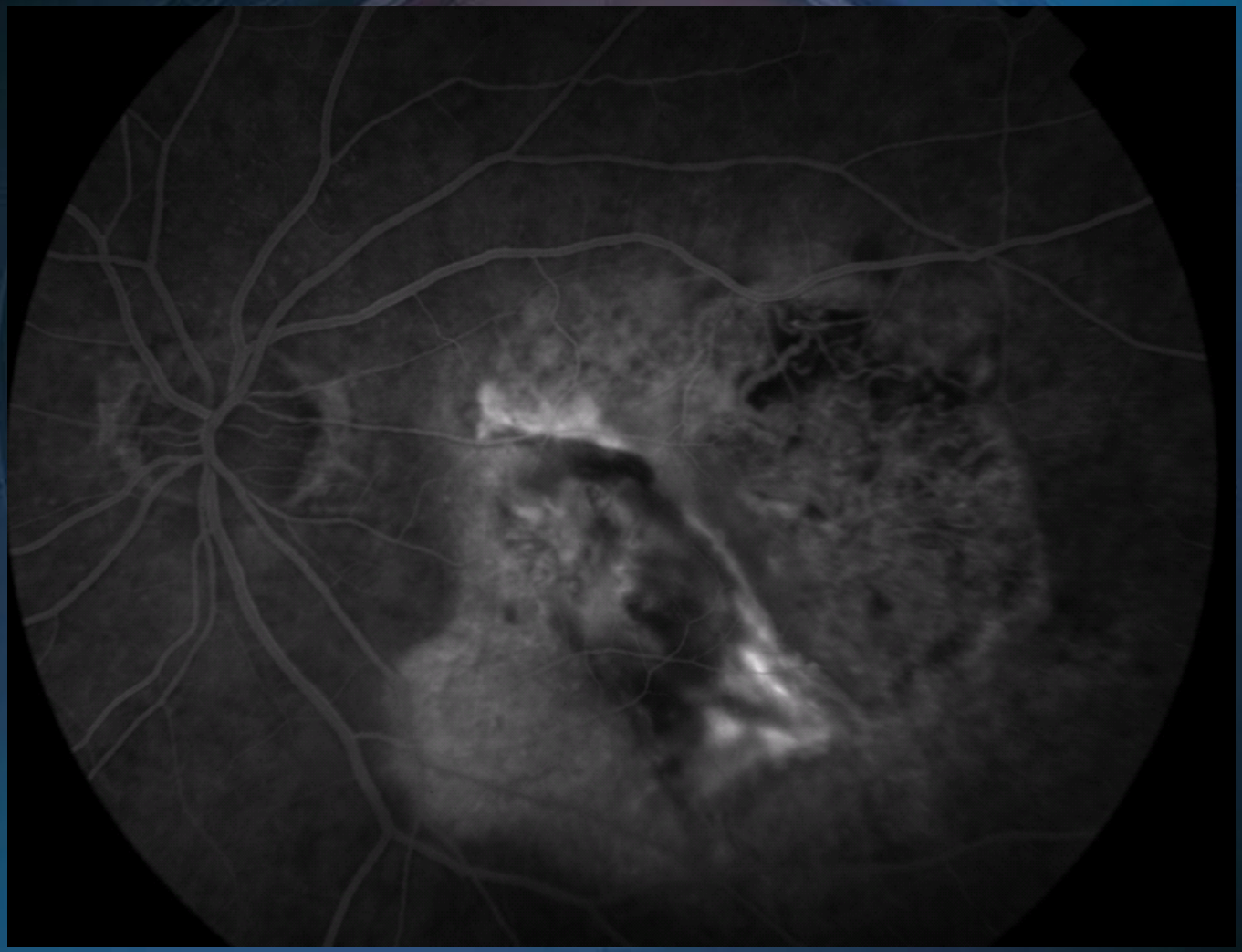


Continuing to Treat or Not ?




The Fellow Eye…
Untreated.

Three Years, and 7 IVT Later…
VA 20/60



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Anti-VEGF Therapy

Retinal Detachment

- VISION (Macugen) 0.08%
- MARINA (Lucentis) 0.00%, 2 yr data
- ANCHOR (Lucentis) 0.36%

- Low rates, similar to natural history

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Anti-VEGF Therapy

Other Complications

- Ocular Hemorrhages
  - 2.9% - Repeated injections in anticoagulated patients
  - (Dayani PN, Am J Ophthalmol, 2007 Sep)
- Submacular Hemorrhages
  - (Goverdhan SV, Br J Ophthalmol 2008 Feb)
- Intraocular Pressure Changes
  - (Hollands H, Can J Ophthalmol, 2007 Dec)
- Advanced glaucoma: transient significant IOP rise
  - (Frenkel RE, Am J Ophthalmol, 2007 Jun)

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Anti-VEGF Therapy

Ocular Complications

1. Bevacizumab (Avastin)
   - PACORES study. 4303 injections, 1310 eyes (1173 pts) (Grafes Arch Clin Nexp Ophthalmol, 2008 Jan)
     - Endophthalmitis 0.16%
     - Tractional retinal detachments: 0.09%
     - Uveitis: 0.02%
     - Rhegmatogenous Retinal Detachments: 0.02%
     - Vitreous hemorrhage: 0.02%

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Anti-VEGF Therapy in:

Retinal Angiomatous Proliferation (RAP)

- Viable treatment option
  - (Ghazi NG, Retina, 2008 May)

Myopic Choroidal Neovascolarization

- No short-term safety concerns (14 patients)
  - (Hernandez-Rojas ML, Retina, 2007 Jul-Aug)

Diabetic Retinopathy

- Traction retinal detachment in severe PDR
  - (Arevalo JF, Br J Ophthalmol, 2008 Feb)

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Caveats

- Polypoidal lesions (PCV): ineffective for diminishing choroidal vascular changes. Additional PDT useful

  (Gomi F, Br J Ophthalmol, 2008 Jan

  Lai TY, Br J Ophthalmol 2008 May)

- Advanced glaucoma: transient significant IOP rise
  - (Frenlkel RE, Am J Ophthalmol 2007, Jun)
- Uveitis
  - (Kumar A, Ophthalmol 2008, Mar)
- Increased foveal thickening after three months without treatment
  - (Melamud A, Am J Ophthalmol Jul 2008)

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Conclusions

- Extremely powerful treatment
- Systemic complications are rare
- Most ocular complications can be prevented with sound clinical management
- Endophtalmitis ...

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Conclusions

The most frequent invasive ocular surgical procedure: cataract

Endophthalmitis after cataract surgery:

- 0.048% (109/225.471) in Sweden
  - (Lundström M, Ophthalmol 2007, May)
- 0.0017% Endophtalmitis Study Group ESCRS
  - (J Cataract Refract Surg 2007, Jun)
- 0.052% Japanese Society Ophthalmic Surgeons
  - (Acta Ophthalmol Scand 2007, Dec)

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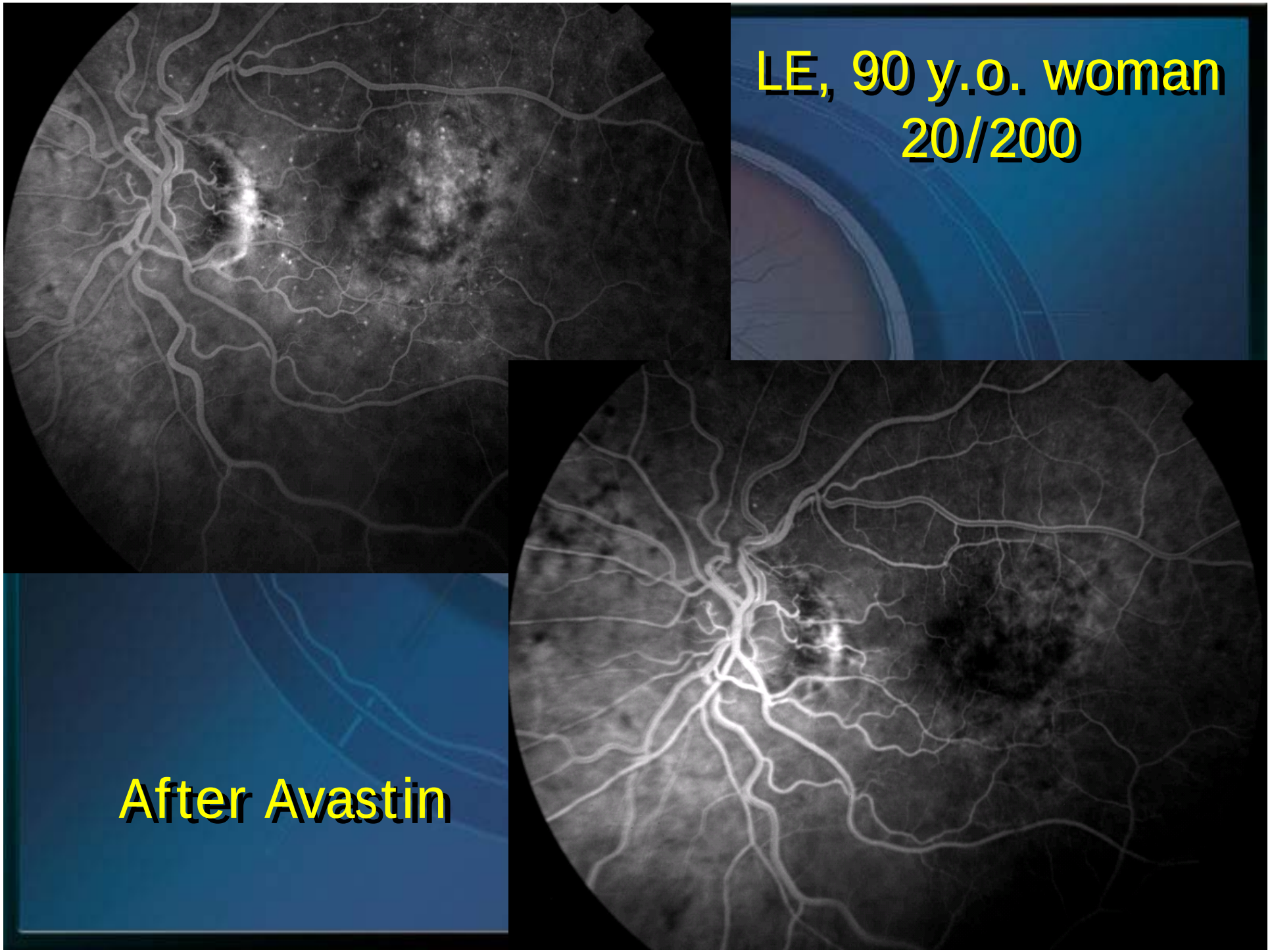
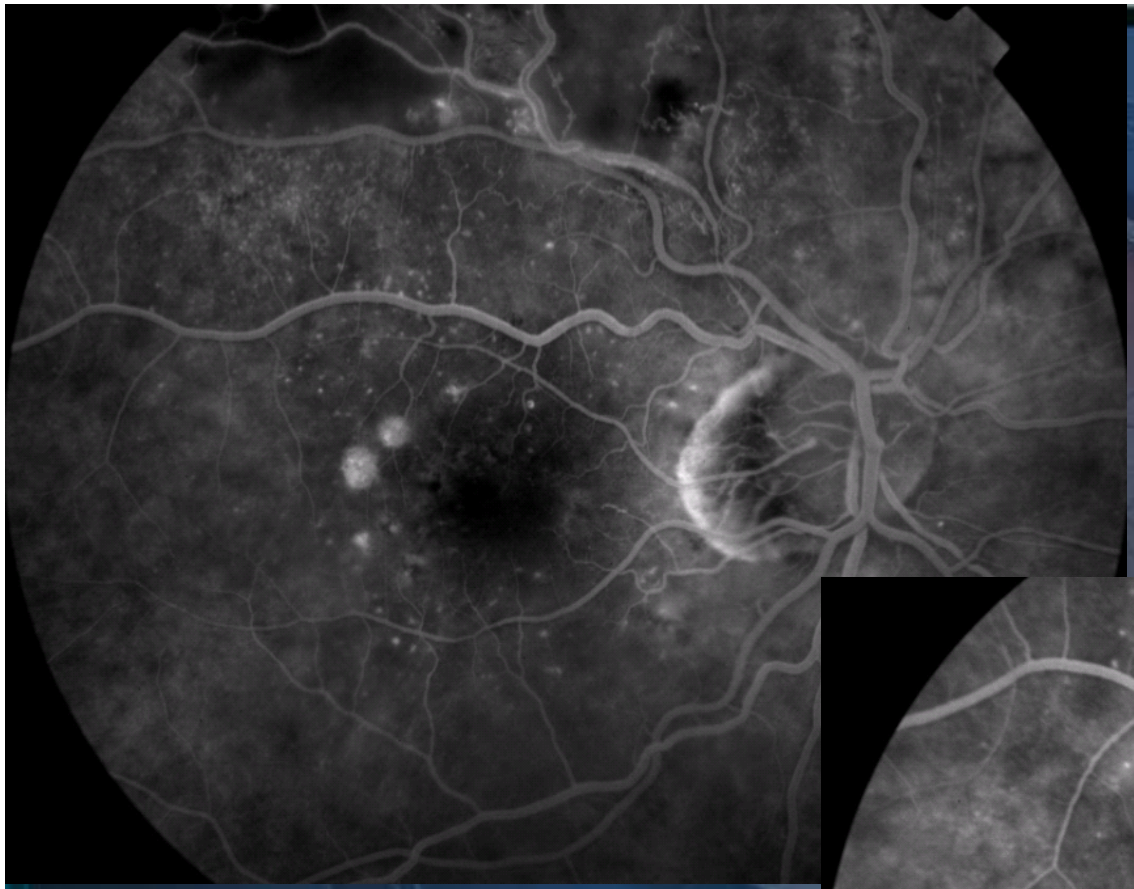

LE, 90 y.o. woman
20/200
After Avastin



RE, 20/25, one month later…

…no longer !