

Age-Related Macular Degeneration

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AMD

- Emerging risk factors
 - Age¹
 - Race¹
 - Smoking²
 - Family history³
 - Variation in the complement factor H gene⁴⁻⁶ and other genes⁷
- Possible initiating events⁸
 - Hypoxia
 - Nutrient deprivation
 - Trauma to Bruch's membrane
 - Infection, inflammatory response
 - Oxidative stress to the retina and retinal pigment epithelium (RPE)



1. Haines et al. Arch Ophthalmol. 2005;123:542. 2. Khan et al. Br J Ophthalmol. 2004;88:75. 3. Bhui et al. Arch Ophthalmol. 2004;122:1491. 4. Klein et al. Science. 2005;308:385. 5. Blainey et al. Science. 2005;308:679. 6. Ripstein et al. Arch Ophthalmol. 2005;123:1587. 7. Ripstein et al. Arch Ophthalmol. 2005;123:1587. 8. Bales et al. Comp Clin Exp Ophthalmol. 2006;24:770.

Historical Perspective - AMD

- Natural history of wet AMD - poor
- 1980s - MPS laser
- Early 2000s - PDT (Visudyne)
- December 2004 - Macugen approved
- May 2005 - First intraocular Avastin injection
- June 2006 - Lucentis approved
- Late 2009 - Options!!!

Genetics - AMD

- Simple
 - Caucasian
 - Light eyes
 - Familial inheritance

Genetics - AMD

- Complex
 - 2005: Complement Factor H (CFH)
 - Common variation
 - Increased susceptibility to dry AMD
 - 2006: Two additional genes
 - Complement factor B
 - LOC gene

Genetics - AMD

- Complement Factor H
 - RPE cells damaged via complement activation
 - Increased levels of C-reactive protein in choroid of patients with CFH polymorphism

Johnson PT, Betts KE, Radeke MJ, Hageman GS, Anderson DH, Johnson LV. Individuals homozygous for the age-related macular degeneration risk-conferring variant of complement factor H have elevated levels of CRP in the choroid. Proc Natl Acad Sci U S A. Nov 14 2006;103(46):17456-61.

Dry versus Wet AMD

- Dry
 - Majority of cases
- Wet
 - Majority of vision loss

Drusen

- Hallmark of dry AMD
- Complex composition
 - Vitronectin
 - Lipids
 - Inflammatory related proteins
 - Amyloid associated proteins

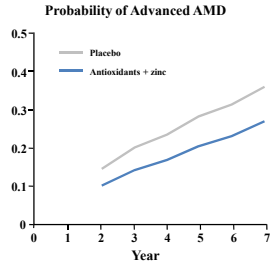


Dry AMD trials (Drusen)

- AREDS II (NEI) AMD Progression

Progression from Dry AMD to Advanced AMD

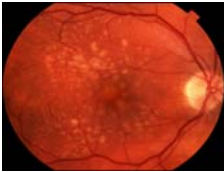
- AREDS¹: over 5 yrs, Category 3 & 4 dry AMD patients taking antioxidants & zinc had a 20% probability of converting to advanced AMD compared to 28% for placebo patients



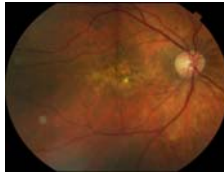
1. AREDS Research Group. Arch Ophthalmol 2001;119:1417-36.

Dry AMD - Drusen

- Photos of patients



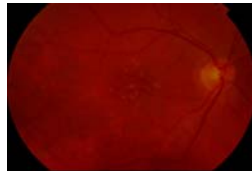
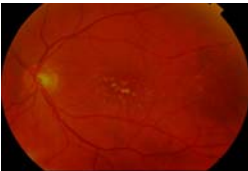
Drusen



Confluent Drusen

Dry AMD – focal drusen

- More photos of patients

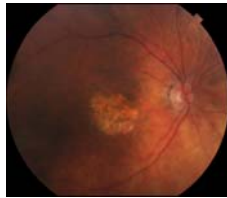


Focal Drusen

AMD – PED and RPE atrophy



Central Serous PED

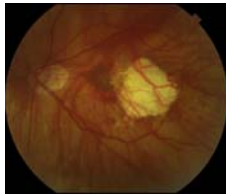


Central GA

Other images



CNV



Myopic GA

Geographic Atrophy

- Severe form of dry AMD
- Loss of RPE
 - Leads to loss of overlying photoreceptors
- Active area of basic science and clinical research

Geographic Atrophy

- Othera Omega trial (drop)
 - Vision 20/25 - 20/63
 - GA in one or both eyes (0.5 to 7.0 DD)
 - GA 1000 microns or less from fovea
 - No history of laser, PPV, CNVM

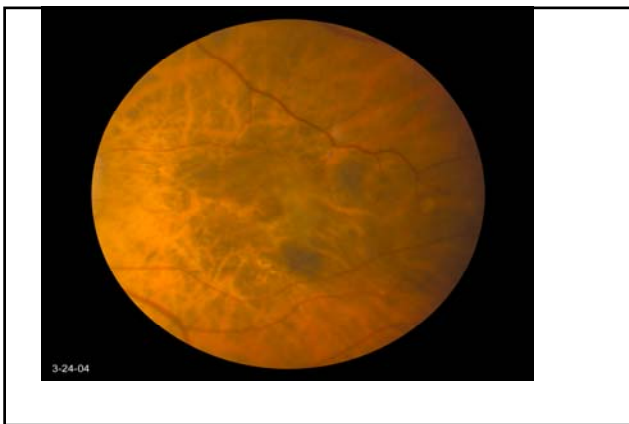
Geographic Atrophy

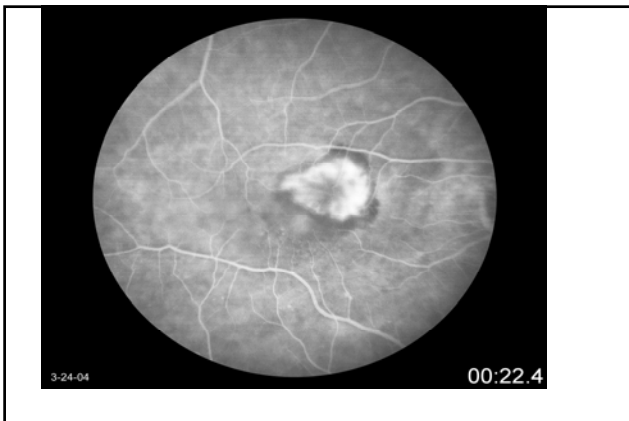
- Sirion trial (pill)
 - Vision 20/20 to 20/100
 - GA 1 to 8 DD
 - GA 250 microns or less from fovea
 - No Lucentis within previous 90 days

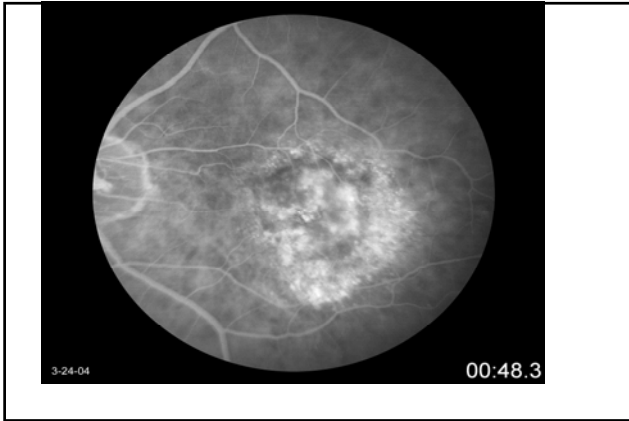
Neovascular AMD

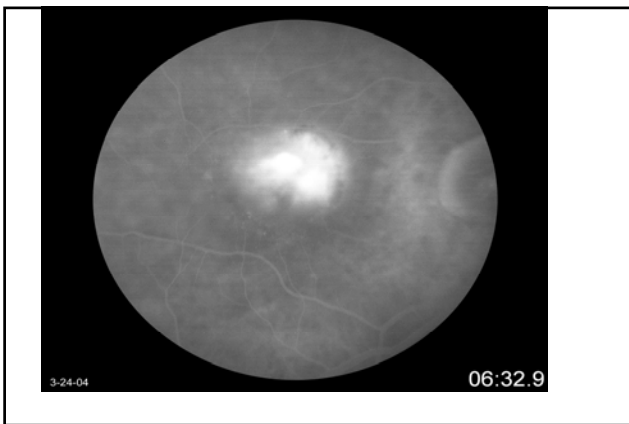
- Case
 - 80 year old woman
 - Decreased vision (OD>OS)
 - Metamorphopsia
 - Va OD: 20/100 OS: 20/30

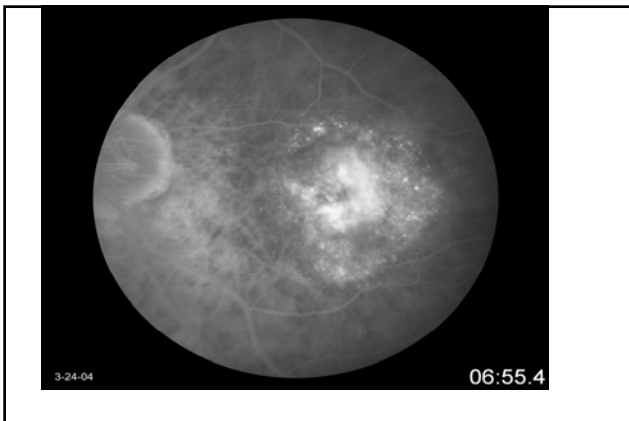


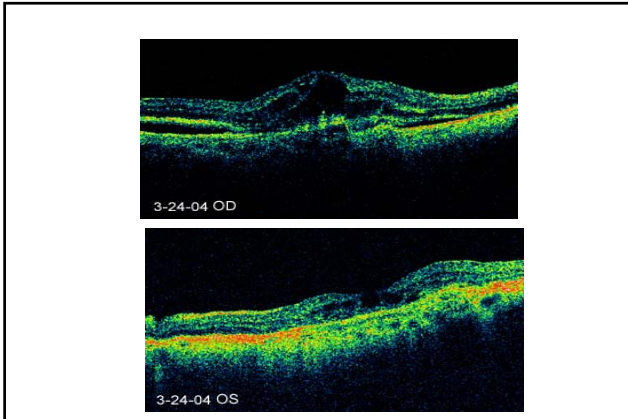












Wet AMD Treatment Options 2004

- Thermal laser
 - Extrafoveal lesions
- Photodynamic therapy
 - Combination therapy (corticosteroids)
- Clinical trials

Wet AMD Treatment Options 2009

- Thermal laser
 - Extrafoveal lesions
- Photodynamic therapy
 - Evolving usage patterns
 - Combination therapy
- Bevacizumab (Avastin)
- Ranibizumab (Lucentis)
- Clinical trials (CATT, HARBOR, others)

Bevacizumab (Avastin)

- Anti-VEGF antibody
- Approved for colorectal cancer (IV)
- Off-label use in ocular neovascular diseases
- Specialty pharmacy prepares doses

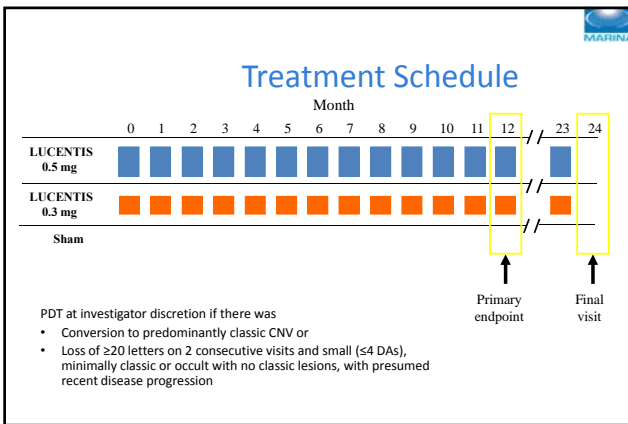
Bevacizumab (Avastin)

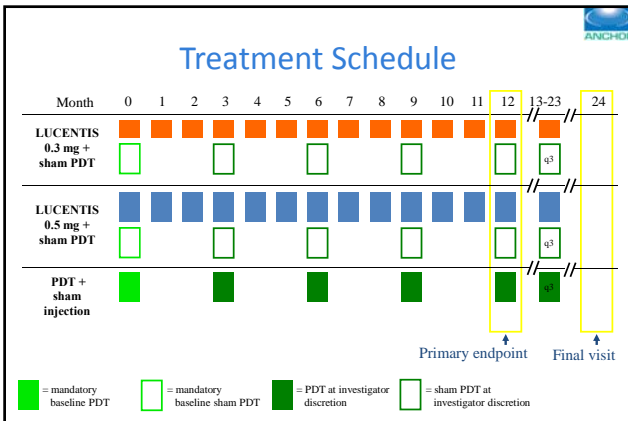
- Small case series very encouraging in wet AMD
- Large price advantage
- Multicenter, NEI-sponsored trial
 - Avastin versus Lucentis
 - Also looking at dosing strategies
 - CATT
 - Actively enrolling patients

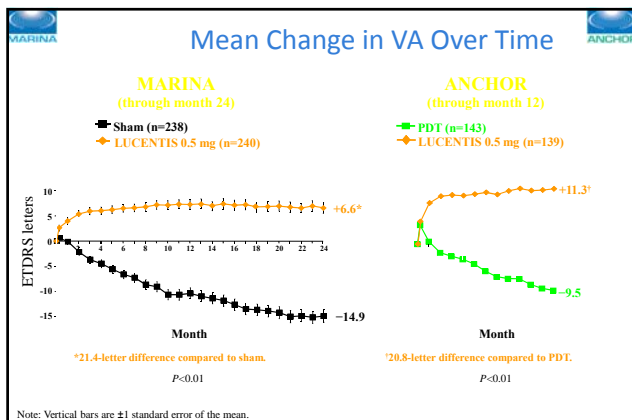
Ranibizumab (Lucentis)

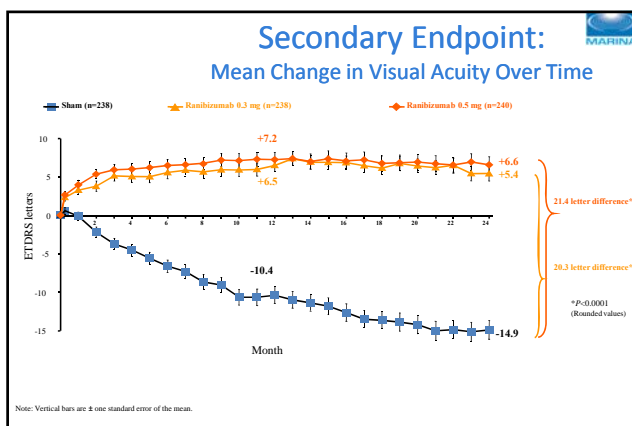
- Anti-VEGF
- Antibody fragment
- FDA-approved for wet AMD (June 2006)
- Groundbreaking results in phase III clinical trials
- Newer trials investigating higher dose (HARBOR)
 - Extended action?

Ranibizumab Trials in Neovascular AMD		
	MARINA	ANCHOR
Lesion Types	Minimally classic or occult	Predominantly classic
Primary Endpoint	% of patients losing <15 letters at month 12	
Key Secondary Endpoints	Mean change in VA over time from baseline through month 12 and month 24 ≥15-letter gainers in VA at month 12 and month 24 compared to baseline Mean change in leakage at month 12 and month 24 compared to baseline	









VEGF Trap – Eye CLEAR-IT 2 Final Primary Endpoint Results

A Phase 2, Randomized, Controlled Dose-
and Interval-Ranging Study of Intravitreal
VEGF Trap-Eye in Patients with
Neovascular Age-Related Macular
Degeneration
