NUTRITION and the EYE

MARCUS RHEM, MD

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DISCLAIMER

- I hold no special degree in nutrition
- This talk by design is very superficial treatment of an entire discipline of medical science
- Nutritional studies are hard to perform
- Correlation is more common than causation
- There is controversy around almost every bend

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GOALS

- Explore a review of human nutrition
- Review the problems with the so-called Standard American Diet
- Review the impact of nutrition on specific ocular situations

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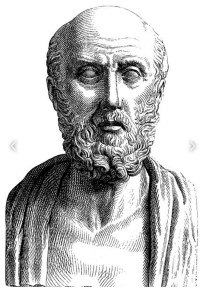
WHAT IS THE ROLE OF NUTRITION?

- "LET FOOD BY THY MEDICINE AND MEDICINE BE THY FOOD."– HIPPOCRATES
- IMPORTANT YET STUDY IS PROBLEMATIC
  - MULTIPLE VARIABLES
  - PROBLEMATIC DATA ACQUISITION
  - OBSERVATIONAL RATHER THAN RCT
  - CORRELATIONS VS CAUSE



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MODERN DEGENERATIVE DISEASES

TYPE II DIABETES MELLITUS	OBESITY	AUTO-IMMUNE DISEASE
AMD	DRY EYE	Genetic and other factors at play • MODIFIABLE RISKS

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Standard American Diet ("S.A.D.")

- Being chronically over-fed
- Consuming highly processed, pro-inflammatory food
  - Refined carbohydrates and sugars
  - Seed oils
  - Some grains
- Damage to the gut microbiome

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PROGRESS…. Doh!!

- HG: active all day, ate available natural food, they slept well and socialized.
- Living well with sudden pitfalls: predation, starvation, trauma
- Now: we sleep less, eat on the run, move less. aging is a slow, steady decline in function

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DISEASES OF PROGRESS

MULTIPLE FACTORS	CORRELATIONS RATHER THAN PROVED CAUSATIONS	PALEOLITHIC CULTURES
• CROWDING • GENETIC • TOXINS • SEDENTARY • SLEEP • NUTRITION		• KITAVAN OF PAPUA NEW GUINEA • TURKANA IN REMOTE KENYA • CANADIAN INUIT (V. STEFANSSON RESEARCH)

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MODERN HUNTER-GATHERER CULTURES

- Absence of DM, obesity, Cardiovascular disease
- Favorable blood lipids
- More diverse gut microbiome
- REVERSED in less than ONE GENERATION

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A BRAVE NEW WORLD: BIG CHANGES

- Hunter-Gatherer
  - Chores. 3 hours
  - Hunting/gathering. 5 hours
  - Social/play. 6 hours
  - Sleep. 10 hours
  - Based on modern H-G cultures
- Modern American
  - Commute. 2 hours
  - Chores. 2.3 hours
  - Screen time. 4 hours
  - Work. 9 hours
  - Sleep 6.7 hours
  - Dept of Labor (pre-Covid)

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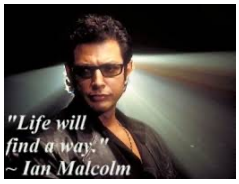
Evolutionary Biology



- Organisms do change over time due to selective pressure
- SEEK a best fit to survival and reproduction

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Discordance Theory

- Organisms develop a set of genes most ideally suited to their environment, activities and needs.
- Changes in environment and activity cause DISCORDANCE requiring adaptation
- Lack of adaptation leads to problems— negative pressure on survivability

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Discordance of human progress

- Agriculture led to food surplus
- Allowed for larger populations, eventually cities;
- Science, industry, medicine, electronics, space travel

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OPTIMUM FORAGING STRATEGY

- GOAL: PROPERLY FED AND NOURISHED WITH ENERGY AND NUTRIENTS MATCHED TO THE NEEDS OF THE ORGANISM AS DETERMINED BY ITS GENETICS.
- HUNTER-GATHERER GENETICS AND GENETIC EXPECTATION
  - OMNIVOROUS: ABLE TO CONSUME WIDE VARIETY
  - FOOD EXPENSIVE TO ACQUIRE AND HARD TO FIND
  - PALATE FATIGUE: WE LIKE VARIETY

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SHORT CIRCUIT

- HYPER-PALATABLE
- ALMOST ENDLESS VARIETY
- SHORT CIRCUITS OUR SATIETY GOVERNOR
- "BETCHA CAN'T EAT JUST ONE…"
- ADDICTION?

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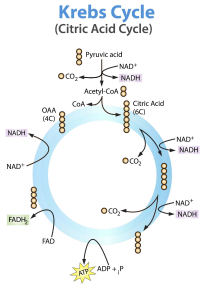
FOOD AND DIGESTION

- MACROS ARE BROKEN DOWN INTO amino acids, fatty acids and sugars
- Undigested fiber and residual starch feed gut bacteria and maintain gut health***
- Hormonal response



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INSULIN

- Regulates blood sugar
- Ideally released in small amounts to deal with carbs
- Chronically high insulin leads to down-regulation of receptors and insulin resistance
  - EVEN MORE insulin to deal with carbs
  - LEADS TO BLOOD SUGAR CRASH.
  - WIDE SWINGS lead to further insulin resistance

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GLUCAGON, Adrenaline, Cortisol

Anti-insulin hormone	Released by hunger and protein consumption	Stimulates gluconeogenesis
Stimulates release of stored energy from fat	Adrenaline: release of glucose from liver glycogen	Cortisol: aids in blood glucose control, modulates inflammation

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The Under-fed state: evolutionarily typical

Low insulin, high glucagon, adrenaline and cortisol → Glucose released from the liver → Fat is released from fat cells → Selective apoptosis of senescent cells → Ketogenesis

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Over-fed State

- Consistent energy excess: STORAGE → Insulin resistance develops
- Excess fat increases inflammatory signaling → Leptin resistance develops in brain
- Insulin HIGH/Glucagon LOW chronically suppressing prevents use of stored fat. → Inflammation and mitochondria damage

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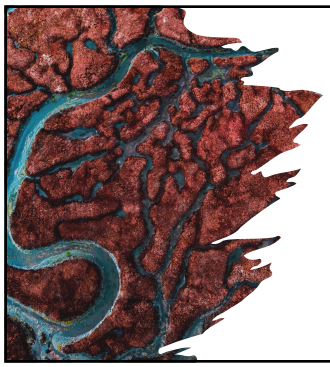

GUT MICROBIOME

- Protects gut permeability
- Controls inflammation
- Critical genetic signaling
- Variety, quantity and location in the large intestine are all important.
- Diets rich in fiber and residual starch feeds microbiota properly and preserves gut lining
- Cellular carbs (fruit, veg) digest later

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SIBO (small intest bacteria overgrowth)

- Refined carbs alter the microbiome
- Alters permeability allow lipopolysaccharide to enter (toxin)
- Increased blood glucose and circulating ffa
- Chronic inflammatory state
- Doesn't require OVERFEEDING just a pro-inflammatory diet

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NEOLITHIC pro-inflammatory foods

- Hard for humans to digest
- Increase the permeability of gut
- Allergens for some
- Inflammatory cytokine
- Glutens, sugar and refined carbs, processed seed oils high in omega-6
- Correlation of glutens with RA, lupus, MS

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Mechanisms of Injury

Overfeeding and refined carbohydrates	Immunogenic Foods	Genetic role of microbiome
• Impairs insulin and leptin sensitivity • Chronic inflammation • Alters gut microbiome	• Damage gut lining • Alter gut microbiome genetic signaling • Mitochondria damage	• Largely ignored until recently

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HUMAN GUT MICROBIOME PROJECT

70% OF THE HUMAN IMMUNE SYSTEM

OVER 1000 SPECIES CONTRIBUTING 10 TIMES THE AMOUNT OF GENETIC MATERIAL AS OUR OWN GENOME

IMPACTS AUTO-IMMUNE DISEASE SUCH AS MS, TYPE 1 DM, RA, AS AND CORONARY ARTERY DISEASE

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UVEITIS

- Horai R et al IMMUNITY 2015; 43--- gut MB linked to EAU
- Horai R, Caspi, RR; FRONT IMMUNOL 2019; 10– diseased patients had less gut diversity and fewer anti-inflammatory microbes than controls
- Ye, Z, et al GUT MICROBES 2020– VKH patients had dysbiosis corrected by immunomodulary treatment
- Phoebe Lin, MD, PhD: changes in gut permeability associated with severity and possibly pathogenesis of ocular inflammation

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AMD

- Various inflammatory pathways
  - Complement
  - Oxidative damage
  - Loss of protective macula pigments
  - Diet high in omega-6 is a proposed mechanism
  - Clearly a genetic component
  - Alterations in gut microbiome may activate inflammatory pathways

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AMD

- Rowan S et al PROC NAT ACAD SCI US 2017 – high glycemic diet in mice led to photoreceptor loss and RPE atrophy which was reversed by low-glycemic diet and led to increased levels of AMD protective features in gut
- Kiang et al IOVS 2017– patients with AMD had changes in metabolic pathways and gut bacteria vs controls
- AREDS1 and AREDS2: studied and demonstrated effects of supplementation
- Carotenoid supplementation may protect loss of photopigments in the macula: Wu et al JAMA OPHTH 2015 Dec

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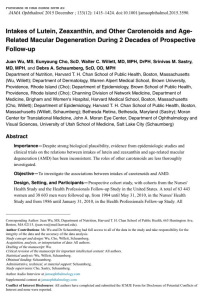
AMD and Carotenoids

HIGHER INTAKE OF LUTEIN/ZEAXANTHIN IS ASSOCIATED WITH A REDUCED RISK OF ADVANCED AMD



JAMA Ophthalmol. 2013 December ; 131(12): 1435–1424. doi:10.1001/jamaophthalmol.2013.5396.

Intakes of Lutein, Zeaxanthin, and Other Carotenoids and Age-Related Macular Degeneration During 2 Decades of Prospective Follow-up

Joan Wu, MS, Eunyoung Cho, ScD, Walter C. Willett, MD, MPH, DrPH, Srinivas M. Sastry, MD, MPH, and Debra A. Schaumberg, ScD, OD, MPH

Abstract

Importance—Despite strong biological plausibility, evidence from epidemiologic studies and clinical trials on the relations between intakes of lutein and zeaxanthin and age-related macular degeneration (AMD) has been inconsistent. The roles of other carotenoids are less thoroughly investigated.

Objective—To investigate the associations between intakes of carotenoids and AMD.

Design, Setting, and Participants—Prospective cohort study, with cohorts from the Nurses' Health Study and the Health Professionals Follow-up Study in the United States. A total of 63 443 women and 38 603 men were followed up, from 1984 until May 31, 2010, in the Nurses' Health Study, and from 1986 until January 31, 2010, in the Health Professionals Follow-up Study. All

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AMD and carotenoids

- CAREDS Study: Variants in genes related to lutein and zeaxanthin status were associated with AMD in CAREDS, adding to the body of evidence supporting a protective role of lutein and zeaxanthin in risk of AMD.
- Studies of macula pigment optical density show lower density in advanced AMD and may be somewhat reversible with supplementation.

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AMD and Carotenoids

- Kale
- Spinach
- Collards
- Turnip greens
- Potentially SUPPLEMENTABLE

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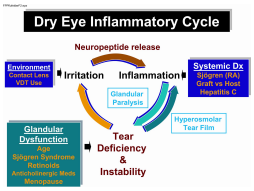
Dry Eye

- Inflammatory in nature
- Worse in auto-immune disease
- Worse in DM
- Responds to anti-inflammatory treatment
- Role of gut in mice?



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Dry Eye

- Wang et al In J Mol Sci; 2018– Inflammatory dry eye in germ free mice.
  - More severe phenotype
  - When placed with healthy mice, they eat each others' feces
  - Germ free mice improve
  - Inflammation and the gut as pathways suggest a role for overall nutrition.

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What to do?

- LIVE A GOOD LIFE– Ron Gross, MD
  - Eat well
  - Get some exercise

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BE INTENTIONAL

- Be normally fed and properly nourished
- Eat whole foods
- Avoid foods that are inflammatory and alter the gut
- Supplement appropriately

- Sugar/Processed carbs
- Highly processes omega - 6 rich foods
- Glutens
- Alcohol
- INDIVIDUAL VARIABILITY

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Supplement

You cannot completely overcome a bad diet, so modify that to the extent its possible	Omega-3	Carotenoids:
	• Simply put, omega-6 is pro-inflammatory and omega-3 is anti-inflammatory • Highly-processed seed oils are high in omega-6 • Seek high quality, third party tested • EPA and DHA	• lutein, zeaxanthin, meso-zeaxanthin • Variable bio-absorption

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Summary

- Modern life is DISCORDANT to our hunter-gatherer genetics
- Rise of inflammatory diseases not found in paleolithic or modern hunter-gatherer communities.
- Modern lifestyle encourages an over-fed sedentary state
- Over-fed state promotes insulin resistance and DM
- Pro-inflammatory foods may play a role in leaky gut, small intestine bacteria over-growth and altered immune and genetic signaling

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Summary

- Poor nutrition plays a role in DM, chronic inflammation, and altered gut microbiome
- The impact of DM on modern eye care is significant
- There is a likely role of chronic inflammation in eye diseases such as uveitis, AMD and dry eye
- We should advise our patients to be intentional: eat a whole food diet and avoid sugar and junk food
- Consider supplementation

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ARMD Update

Specialty Eye Institute

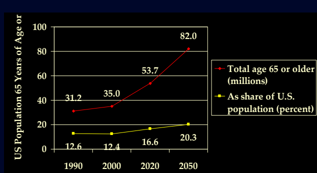
William Rhoades, MD

I have no financial disclosures.

AMD: The Graying of America

- Year 2000 – 1.75 million with AMD
- Year 2020 – 2.95 million with AMD, up 59%
- The incidence of advanced AMD (wet AMD or severe dry AMD) increases with age
- AMD is the number one cause of vision loss in the over 65 age group

AMD: The Graying of America



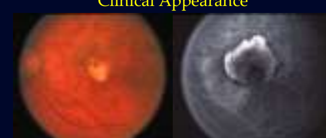
Rogers CC Food Review. Economic Research Service, USDA 2002;25:2-7.

Diagnostic Exam and Testing

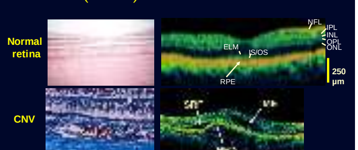
- Visual acuity
- Slit lamp biomicroscopy
- Fundus color and red-free photos
- Fundus autofluoresence
- Fluorescein angiography
- Optical coherence tomography

Diagnostic Testing Fluorescein Angiography

Clinical Appearance



Optical Coherence Tomography (OCT) in Wet AMD



Normal retina sample courtesy of Wilmer Eye Institute, Johns Hopkins School of Medicine; Baltimore, Maryland.
OCT images courtesy of Bascom Palmer Eye Institute. University of Miami School of Medicine; Miami, Florida.
SRF = subretinal fluid; PED = pigment epithelial detachment; ME = macular edema.
Green and Enger. *Ophthalmology*. 1993:100:1519; Copyright © 1993 Elsevier, Inc. All rights reserved.

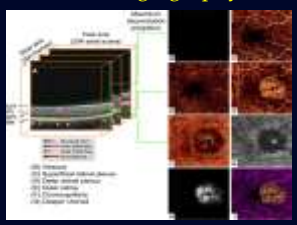
Retinal Layers – OCT
(Optical Coherence Tomography)

Spaide, Retina Sept. 2011

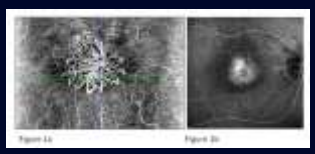
OCT Angiography

- Non invasive technology
- Motion contrast imaging to generate volumetric blood flow information
- Presently an adjunct to FA

OCT Angiography



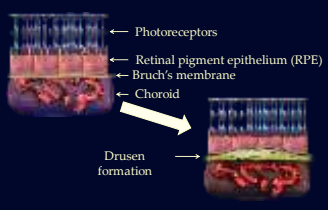
OCT Angiography



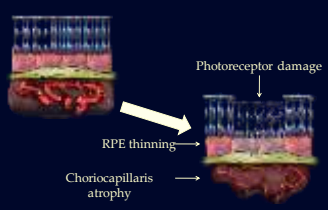
Dry AMD - Risk Factors

- Genetic predisposition
- Smoking history
- High blood pressure
- Elevated cholesterol levels
- Cardiovascular disease

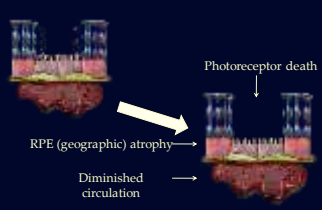
Dry AMD - Development



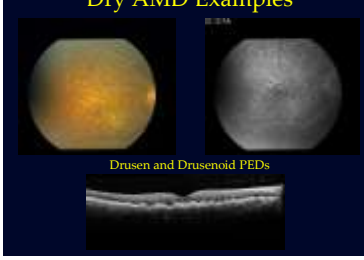
Dry AMD - Development



Dry AMD - Development

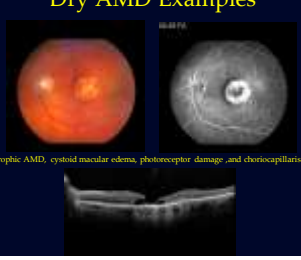


Dry AMD Examples



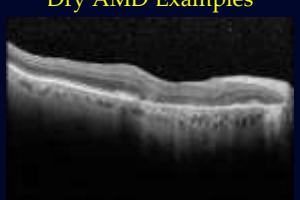
Drusen and Drusenoid PEDs

Dry AMD Examples



Atrophic AMD, cystoid macular edema, photoreceptor damage ,and choriocapillaris loss

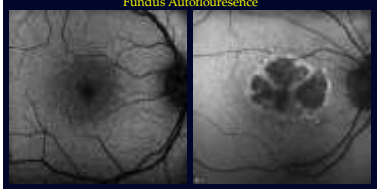
Dry AMD Examples



Atrophic AMD with Geographic Atrophy, Drusen and Photoreceptor Loss

Dry AMD Examples

Fundus Autoflouresence



Normal Geographic Atrophy

AREDS 2 Formulation

- Vitamin C (500 mg)
- Vitamin E (400 IU)
- Beta Carotene (15 mg)
- **Lutein (10 mg)/Zeaxanthin (2 mg)**
- Zinc (80 mg zinc oxide)
- Copper (2 mg cupric oxide)
- **Omega-3 fatty acids (DHA/EPA)**

AMD: Age Related Macular Degeneration

- Dry Macular Degeneration – accounts for 90% of AMD and 10% of severe vision loss
- **Wet Macular Degeneration** – accounts for 10% of AMD and 90% of severe vision loss

Wet AMD - Development

Drusen development and Bruch's membrane thickening

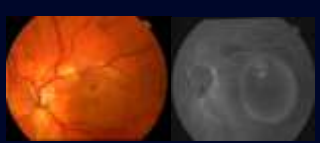
Wet AMD - Development

Choroidal Neovascularization through Bruch's membrane

Wet AMD - Development

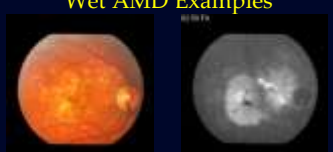
Hemorrhaging and edema

Wet AMD Examples



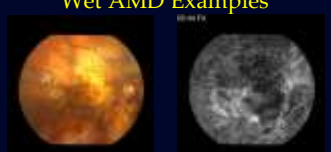
Pigment epithelial detachment

Wet AMD Examples

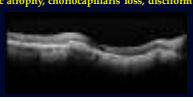


Drusen, Drusenoid PEDs, Serous PED, CNV

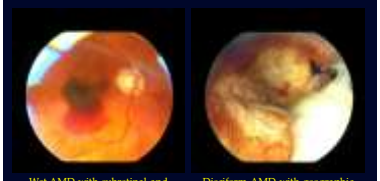
Wet AMD Examples



Geographic atrophy, choriocapillaris loss, disciform wet AMD



Wet AMD Examples



Wet AMD with subretinal and subRPE hemorrhages

Disciform AMD with geographic atrophy

Treatment Options for Wet Macular Degeneration

- Observation
- Thermal laser
- Cold laser (Photodynamic therapy)
- Steroid injection
- Anti-VEGF therapy
- Investigational

Treatment Options for Wet Macular Degeneration

- Observation
- Thermal laser
- Cold laser (Photodynamic therapy)
- Steroid injection
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- Investigational

Thermal Laser

- Oldest effective treatment
- Leaves permanent scar and blind spot
- High rate (>50%) of regrowth of the blood vessels
- Common visual outcome 20/200 to 20/400

Treatment Options for Wet Macular Degeneration

- Observation
- Thermal laser
- Cold laser (Photodynamic therapy)
- Steroid injection
- Anti-VEGF therapy
- Investigational

Photodynamic Therapy (PDT)

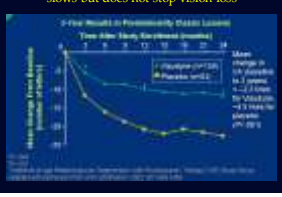
- Visudyne administered intravenously
- Attaches preferentially to the endothelium of abnormal blood vessels

Photodynamic Therapy (PDT)

- Laser activates the drug
- Injures the blood vessel walls (endothelial cells)
- The abnormal vessels clot
- Given as an every three month treatment

Photodynamic Therapy (PDT)

PDT with Visudyne (Verteporfin) slows but does not stop vision loss



Treatment Options for Wet Macular Degeneration

- Observation
- Thermal laser
- Cold laser (Photodynamic therapy)
- Steroid injection
- Anti-VEGF therapy
- Investigational

VEGF: The Molecule

- The VEGF family of molecules includes placental growth factor (PlGF), and VEGF A/B/C/D/E
- Originally known as vascular permeability factor (VPF) and endothelial cell growth factor (ECGF)
- VEGF-A first purified by Ferrara and Henzel in 1989

Properties of VEGF-A

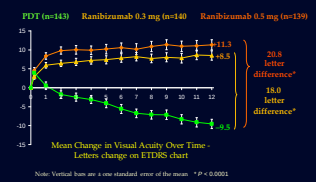
- Involved in both normal and pathologic vascular processes
- Expressed at high levels in response to hypoxia
- Smaller isoforms are freely diffusible, while larger isoforms are bound to the basement membrane or cell surface via heparin sulfates
- Endothelial cell-specific mitogen, promoting angiogenesis
- Greatly increases microvascular permeability

Angiogenesis Inhibitors

VEGF Inactivation

- Neutralizing antibody – Bevacizumab, Avastin
  - Binds to all VEGF-A isoforms
  - Developed for systemic malignancies in parallel with Ranibizumab
  - Originally FDA approved for intravenous use in colorectal cancer, and now other cancers
  - Intravitreal delivery

Anti-VEGF Therapy for Wet Macular Degeneration - Results

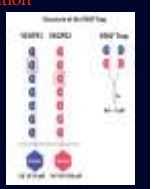


Note: Vertical bars are ± one standard error of the mean * $P < 0.0001$

Angiogenesis Inhibitors

VEGF Inactivation

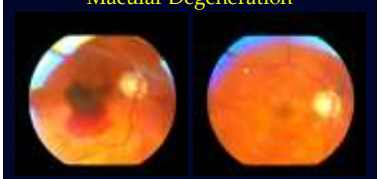
- VEGF trap, decoy receptor
  - "Aflibercept" (Eylea)
  - Intravitreal injection
  - A fusion protein of VEGFR-1 and -2 extracellular domains with human IgG (Fc portion)
  - Human amino acid sequences
  - Smaller than an antibody (MW ~110,000)
  - Binds VEGF more tightly than native receptors, monoclonal antibodies or aptamers
  - Blocks all VEGFs and placental growth factor (PlGF)



Anti-VEGF Therapy for Wet Macular Degeneration

Before Ranibizumab | After Ranibizumab

Anti-VEGF Therapy for Wet Macular Degeneration



Before Ranibizumab | After Ranibizumab

Comparison of Age-related Macular Degeneration Treatments Trials (CATT)

CATT Clinical Sites

- **1185 patients with neovascular AMD enrolled at 43 sites in the United States**

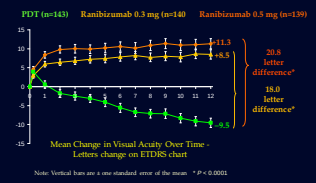
ARMD treatment trials

CATT, ANCHOR, MARINA, VIEW1, VIEW2, TREX-AMD, IVAN, SUSTAIN, SAILOR, HORIZON, HARBOR, RANGE, SEVEN-UP, and more

Studies determine safety, efficacy, and treatment strategy

- "Doc, how many injections do I need?"

Anti-VEGF Therapy for Wet Macular Degeneration - Results



Injection Treatment Strategies

- Monthly dosing
  - gold standard
- Treat and Extend
  - practical, real world approach with good result
- Pro Re Nata (PRN)
  - Poorer outcomes, more likely to have lesion growth/FA leakage

- "Doc, will I get my vision back?"
  - 90% will maintain acuity
  - ~30% will gain vision once treatment started, usually in first 3 months
  - Smaller lesions/early diagnosis more likely to achieve gains

- "Doc, isn't there an eyedrop that could solve my problem?"

Angiogenesis Inhibitors

Matrix Metalloproteinase Inhibitors (MMPIs)

- Squalamine lactate
  - Natural aminosterol originally isolated from the dogfish shark
  - Thought to inhibit mitogen-induced proliferation and migration of endothelial cells
  - Currently being studied as an adjunct to treatment of wet AMD (eye drops): Ohr-002
  - Also used as a systemic versus intravitreal delivery

- Doc, isn't there a drug that lasts longer?"

- LADDER trial
  - Surgically placed refillable reservoir
- Brolucizumab – Alcon
  - Smallest anti-VEGF molecule
  - ?12 week duration
- Darpin – Allergan
  - Small recombinant protein
  - ?12 week duration

Thank You