UPDATE ON AMD

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Disclosures

- Speakers bureau and/or Advisory Board for:
  - Alcon
  - Allergan
  - B&L
  - Heidelberg
  - Macula Risk
  - MacuLogix
  - ThromboGenics
  - Nicox

Introduction

- Exciting time to be interested in AMD
- Many new treatments now available for AMD
  - Years ago, we had nothing at all to offer patients with AMD
- Current Treatments
- Potential Treatments
- New Diagnostic Equipment

Dry AMD

- Currently mainstay treatment for Dry AMD revolves around prevention of progression through vitamins, nutrition and lifestyle changes
  - Rheophoresis, Laser, Anecortave Acetate did not prove effective
- Early detection of conversion from dry to wet may result in better treatment for patients

AREDS 2

- AREDS 2: Enrollment ended June 2008 with ≈4200 patients followed for six years
  - Effect of lutein, zeaxanthin and omega 3 on AMD
  - Effect of eliminating beta carotene on AMD
  - Effect of reducing zinc on AMD
  - Effect of supplements on cataracts
  - Validate the AMD scale from original AREDS
- Results released May 5, 2013

AREDS2 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)~~

Wet AMD

- Various agents currently being used as intravitreal injection
  - Macugen® (pegatanib sodium) Dec 2004
  - Lucentis (ranibizumab) June 2006
  - Avastin (bevacizumab) Not FDA approved
  - Eylea (aflibicert) Nov 2011

Macugen® (pegatanib sodium)

- Anti-vasoactive endothelial growth factor (VEGF) aptamer
  - Developed by OSI Pharmaceuticals, co-marketed with Pfizer
  - Delivered by intravitreal injection
- FDA Approved December 2004
  - Commercially available February 2005
- VISION Study
  - Intravitreous injections of 0.3 mg, 1.0 mg and 3.0 mg every 6 weeks for 48 weeks (8 injections)
    - Loss of less than 15 letters 70% with tx vs 55% w/ o tx
    - 33% maintain or lost vision with tx vs 23% w/o tx

Macugen

- Macugen has been widely supplanted by newer agents
  - Most notably Lucentis and Avastin
- Must be injected every 6 weeks for 2 years
  - Eight to nine injections /year may be indicated
  - Cost: VA medication alone is $780. Most places $1200 med plus fees

Lucentis (ranibizumab)

- Antibody fragment which blocks VEGF activity
  - Less specific than Macugen, so perhaps more efficacious
- Delivered by intravitreal injection
- Developed by Genentech and marketed by Novartis
- FDA Approved June 30, 2006

Lucentis

- ANCHOR Study (classic CNVM)
  - 2 Year Phase 3 randomized study
    - 94% of pts treated with 0.3 mg had stable or improved vision vs 64% with Visudyne
    - 36% had gain of 15 letters or more
    - Avg acuity gain was 11.3 letters vs 9.5 letters lost with Visudyne at one year
    - 31% had VA of 20/40 or better vs only 3% with Visudyne
- MARINA Study (minimally classic/occult)
  - 95% of treated pts vs 62% of controls had less than 15 letter loss
  - 25% treated vs 4.6% of controls had 3 line gain
  - At 2 yrs, 6.6 letter gain with tx vs 14.9 letters lost without

Lucentis

- Results were promising, with better results than Macugen
  - For first time, results showed an actual increase in vision in treated vs untreated group
- Recommended injection: every 4-6 weeks for 2 yrs
- Cost: approx $2500 for medication alone

Lucentis

- Additional studies, PRONTO and PIER, looking at alternative dosing schedules
  - PRONTO: one injection/mos x 3. Then inject based on clinical or OCT findings
  - PIER: one injection /mos x 3. Then inject q 6 months for 2 years
- Results were very similar to original studies, especially with PRONTO

Avastin (bevacizumab)

- Drug currently FDA approved for the treatment of metastatic colorectal cancer and certain lung cancers (Genentech)
  - Parent drug of Lucentis. Originally thought to be too large to penetrate retina
- Currently widely used as treatment for CNVM due to its anti-VEGF properties

Avastin

- First report of intravitreal injection in May 2005
- First case reports published in July 2005
- Within 6 months, global acceptance and widespread clinical use
  - despite lack of large scale studies regarding efficacy, safety and dosing

Avastin

- Major advantage is COST
  - $15-$50 per 0.3 ml injection
    - 1/40 cost of Lucentis
  - Approx $1k for Macugen/$2.5K for Lucentis
- Issue is there are no large prospective study to judge its efficacy and safety
  - Systemic concern is thrombolytic events
    - Amount used in vitreous is 300-400 fold lower than that administered IV
- Some controversy remains but continues to be used widely

Avastin

- No studies yet to indicate proper dosing
  - Most often, one injection/mos x 3 mos.
  - Then repeat FA/OCT and evaluate for additional treatments
  - Also, no h/o MI or CVA within 6 mos
- Pt must be informed of its off-label use
- Dangers reported regarding compounding

Avastin vs. Lucentis

What is the Treatment of Choice?

- Complications of Age-Related Macular Degeneration Treatment Trial (CATT)
  - NEI/NIH sponsored trial
  - First year results released May 1, 2011 NEJM
- 1208 patients randomized
  - Lucentis with 4 week dosing
  - Avastin with 4 week dosing
  - Lucentis with variable dosing (PRN)
  - Avastin with variable dosing (PRN)

CATT: 1 yr results

- Equivalent effects on visual acuity with same administration
  - Lucentis monthly 8.5 letters gained
  - Avastin monthly 8.0 letters gained
  - Lucentis PRN 6.8 letters gained
  - Avastin PRN 5.9 letters gained

CATT: 1 yr results

- Central retinal thickness:
  - Greater effect in Lucentis monthly group (196um decrease) than in other groups
    - 164 um Avastin monthly
    - 168 Lucentis as needed
    - 152 Avastin as needed
  - Fluid on OCT
    - At 4 weeks, no fluid in 27.5% of pts w/ Lucentis vs. 17.3% with Avastin
    - At 1 yr, no fluid in 43.7% Lucentis monthly 19.2% Avastin PRN

CATT: 1 yr results

- Adverse effects
  - When dosing regimens combined, slightly more serious adverse events in Avastin group
    - 24.1% for Avastin
    - 19.0% for Lucentis
    - Risk ratio 1.29 for avastin as compared to Lucentis

CATT: 1 yr summary

- Vision with Lucentis vs. Avastin relatively equal over course of first year
  - Some evidence of more effect with Lucentis on anatomical structure, ie more decrease in RT on OCT, but did NOT correlate with improved visual function
  - Some hint that less systemic events with Lucentis
  - HUGE cost differential
- Avastin wins most of the time, with select cases benefiting from Lucentis

CATT: 1 yr results

- Average cost for first year treatment:
  - $23,400 for Lucentis monthly
  - $13, 800 for Lucentis PRN
  - $595 for Avastin monthly
  - $385 for Avastin PRN

CATT 2 yr Results

- At end of 2 years, both had similar effects on vision when the dosing regimen was the same
  - Mean gain in acuity, proportion gaining or losing 3 lines, % better than 20/40 all similar
- Mean gain slightly better for monthly vs. as needed, 2.4 letters
- Rates of death and thrombotic events similar
- Pts with serious systemic adverse effects higher with Avastin (39.9% vs. 31.7%)

CATT 2 yr results

- GA most in Lucentis monthly, but more in both monthly
- Less fluid at 1 and 2 yrs with Lucentis
- Led to 0.6 more injection with Avastin in second yr, 1.5 more over 2 yrs

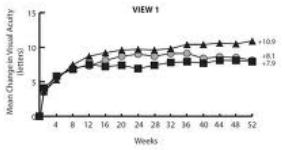
Other studies

- Multiple other comparative studies have confirmed no clinically significant differences between Avastin and Lucentis
  - CATT (US)
  - IVAN (Great Britain)
  - MANTA (Austria)
  - GEFAL (France)
  - BRAMD (Netherlands)
  - LUCAS (Norway)

Eylea

View 1

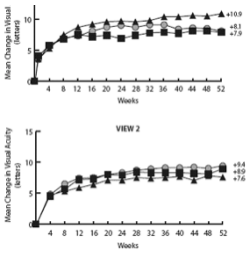
- 95% of pts receiving 2 mg q 2 mos achieved maintenance of vision vs. 94% with Lucentis monthly
- 7.9 letter mean improvement of vision (vs. 8.1 with Lucentis monthly)



Eylea

View 2

- 95% of pts receiving 2 mg q 2 mos achieved maintenance of vision vs. 94% with Lucentis monthly
- 8.9 letter mean improvement of vision (vs. 9.4 with Lucentis monthly)



Eylea

- Cost: Eylea ≈$1850/injection, with injection every 2 months
  - Therefore ½ of Lucentis montlhy
- Second year study will evaluate use PRN

Eylea

- Second year results (unpublished) found virtually similar results when Eylea vs . Lucentis used as needed
  - Elyea 4.2 injections for the year
  - Lucentis 4.7

Is AMD in our DNA?

- AMD is a genetic disease with known markers accounting for at least 70% of the population attributable risk
- Other 30% is environmental/lifestyle
- Risk factors
  - Non-modifiable: age, race, gender
  - Modifiable: Smoking, increased BMI, poor diet/ nutrition, UV exposure

AMD is a Genetic Disease

Population Attributable Risk	
Condition	Genetics (%)
Colorectal Cancer	35
Diabetes II	26
Coronary Artery Disease	40
AMD	70

Those with stronger genetic risk develop more advanced disease earlier in life.

Major genetic factors

- CFH
  - Single most important genetic component
  - CFH Y402H
- ARMS2/HTRA1
  - Second most important gene in AMD
- C3
  - Another component of the complement system
- ND2
  - Mitochondrial oxidative phosphorylation molecule
- Others

Genetic Factors and Risk: More than additive!

- Former Smokers: 1.29x
- Current Smokers: 2.4X
- Non-Smoker and CFH,Y402H: 7.6X
- Current smoker and CFH,Y420H: 34X

AMD Genetic Testing

Macula Risk NXG

Identifies AMD patients who may progress to vision loss within:

- 2 years
- 5 years
- 10 years

Cheek Swab

Clinical Validation March 2012 IOVS

Prospective Assessment of Genetic Effects on Progression to Different Stages of Age-Related Macular Degeneration Using Multistate Markov Models

Yi Yu, Robyn Reynolds, Bernard Rosner, Mark J. Daly, and Johanna M. Seddon

Investigative Ophthalmology & Visual Science, March 2012, Vol. 53, No. 3

2560 Caucasians
Average Follow up = 10.3 years
5 year predictive power = 0.883 'C' Statistic Score
10 year predictive power = 0.895 'C' Statistic Score
Sensitivity & Specificity > 80%
Macula Risk NXG

Primary Eye Care Protocol

Macula Risk® Advisory Panel® Recommendations
Risk Stratification by Macula Risk (MR) Score and Disease Stage

MACULA RISK SCORE	AMD DISEASE STAGE	EXAM FREQUENCY (INTERVALS IN MONTHS)	FUNDUS PHOTOGRAPHY (INF IF AVAILABLE)	OCT	NUTRITIONAL SUPPLEMENTS	AMSLER GRID	REFERRAL TO RETINA SPECIALIST
MR 1-2	Early AMD	12	1/yr	-	+/-	+	-
	Intermediate AMD	6-12	1/yr	1-2/yr	+	+	-
	Advanced Dry AMD	3-6	1-3/yr	2-4/yr	+	+	+/-
	CNV Suspected/Confirmed						+
MR 3	Early AMD	6	1/yr	1-2/yr	+	+	-
	Intermediate AMD	6	1/yr	2-3/yr	+	+	-
	Advanced Dry AMD	3-4	1-3/yr	3-4/yr	+	+	+/-
	CNV Suspected/Confirmed						+
MR 4	Early AMD	4-6	1/yr	2-3/yr	+	+	-
	Intermediate AMD	4	1-2/yr	3-4/yr	+	+	+/-
	Advanced Dry AMD	3-4	2-3/yr	3-4/yr	+	+	+/-
	CNV Suspected/Confirmed						+
MR 5	Early AMD	4-6	1/yr	2-3/yr	+	+	-
	Intermediate AMD	4	1-2/yr	3-4/yr	+	+	+/-
	Advanced Dry AMD	3-4	2-3/yr	3-4/yr	+	+	+/-
	CNV Suspected/Confirmed						+

Recommended practice protocol developed by the Macula Risk Optometry Advisory Board: L. Alexander, D. Cunningham, M. Dunbar, S. Ferrucci, J. Gerson, P. Karpecki, G. Morgan, D. Nelson, J. Rumpakis, J. Schaeffer, L. Semes, D. Shechtman, J. Sherman, K. Smick

AutoGenomics

- Developer of automated multiplexed DNA with more than 50 applications currently
  - Infectious disease, women's health, oncology
- Currently developing and AMD panel looking at over 20 genetic variants
  - CFH
  - ARMS2
  - C2, C3
  - TIMP 3, etc.

Genetics and Treatment

- Ophth 2013 Hagstrom (843 pts)
  - 37% higher risk for additional Lucentis if Y402H CFH
  - CFH TT/TC treated with Avastin had increase in vision with 53.7 % improved vs. only 10.5% if CC genotype
- Ophth Nov 2010 Smailhodzic et al

Genetics and Treatment

- Ophth Nov 2012 Smailhodzic et al
  - If no high risk ARMs 2 /CFH alleles, mean a VA improvement of 10 letters
  - No VA improvement if 4 High risk CFH and ARMS 2 alleles
  - If 6 high risk alleles, lost of 10 letters
  - Patients with high risk alleles were on average 5.2 years younger than those with less high risk alleles

Genetics and Treatment

- Br J Ophthalmol June 2015 Hu et al
  - Meta Analysis looking at response to anti-VEGF treatment in wet AMD
  - 12 carticles, 2389 cases
  - A69S gene in ARMS 2 shown to predict anti-angiogenic response in an East Asian polulation
  - Not found to be predictive in Caucasian subgroups

Genetic Treatment

- If defective gene responsible for abnormal VEGF expression can be localized, perhaps a replacement, or fixer gene can be injected into the eye ONE TIME!
  - Genzyme
  - Avalanche Biotechnologies
  - Oxford BioMedica
  - ForSight Labs
  - NeuroTech

Avalanche Biotechnologies: AAV2

- Viral vector harboring a gene that encodes a protein (sFLT-1/VEGFR-1) for the treatment of Wet AMD
- 8 eyes with wet AMD
  - Injected with Lucentis, then AAVs, then 2nd Lucentis
  - 5/6 with AAV2 gained +8.7 letters (low dose) or +6.3 (high dose)
  - -3.5 letters in control
  - Only 2/6 needed additional injection in first year
- 2a study in Australia underway (32 pts)
- 2b Enrolling in US late 2015

Summary

- Knowledge of genetic risk is important
  - Increased counseling for patients at high risk
  - Know which pts need to be examined more frequently
  - Sooner vitamin supplementation
  - May have implications regarding treatment
  - May lead to new treatments

Potential Therapies

- Currently, there are ≈ 1143 studies evaluating AMD, both Wet and Dry
  - www.clinicaltrials.gov (February, 2015)
- Exciting time to be involved, with many possible therapies out there that may prove useful for our AMD patients

Potential Therapies

- Better Efficacy
  - Better drug
  - Different Mechanism
- Reduced administration
- Different delivery System
  - Eye drops
  - Oral
  - Others
- Earlier Diagnosis

FoVista

- Anti-PDGF agent
- Theory is that when used in conjunction with anti-VEGF agents, will have a better effect due to synergistic effect
- Ophthotech
  - Currently in stage 2b studies

FoVista

- Initial phase 1 trial to show safety
  - 59 % had improvement of three lines or more
- Phase 2b study: 449 patients
  - Fovista/Lucentis combination gained 10.6 letters at 24 weeks, vs. 6.5 with Lucentis alone
    - 62% additional benefit
    - First study to show results BETTER THAN Lucentis

Abicipar Pegol

- Vegf- DARPin: Designed Ankyrin Repeat Protein
  - Allergan
- Binds VEGF A with higher affinity
- Longer half life
  - Potential to last 12 weeks
- Phase II Trials: 25 pts
  - at 20 weeks, mean VA improvement
    - Abicipar Pegol 2mg: 9.0 letters
    - Abicipar Pegol 1 mg: 7.1 letters
    - Lucentis: 4.7 letters

ESBA 1008

- Single chain antibody fragment (scFv)
- Smaller than current agents, yet potentially longer duration
- Alcon/Novartis
- Phase II study: 194 patients
  - ESBA 1008 0.5, 3, 4.5, or 6 mg vs. o.5 mg Lucentis
  - At 1 mos, mean VA improvement
    - 6 mg ESBA 1008: 10.4 letters
    - O.5 mg Lucentis: 6.5 letters

ESBA 1008

- Now Renamed RTH258
- Phase 2 study
  - 6 mg of RTH258 vs. 2 mg Eylea in 90 eyes
  - "Promising visual acuity gains that were non-inferior to Eylea"
  - Well tolerated, no adverse events
  - Perhaps a prolonged duration of action, potentially reduced treatment burden
- Two phase 3 trials will look at RTH258 in about 1700 pts every 3 months

Replenish®

- Replenish® drug delivery pump by Alcon/ Novartis
- Fully programmable, refillable pump
- Rechargeable to support chronic use
- Applicable to back of eye disorders
- May prove alternative to injections
- Looking at with ESBA 1008 Proof of concept

VEGF Eye Drops

- ATG3: a topical eye drop for treatment of wet ARMD
  - Phase II trial will enroll 330 pts to receive two concentrations of ATG3 bid vs placebo for 48 weeks
- GATE Study by Alcon
  - Phase III study evaluating AL-8309B as topical ocular treatment for geographic atrophy secondary to ARMD
- Pazopanib
  - FDA approved for renal cell carcinoma
  - Treatment for wet ARMD
- OT-551
  - Anti-angiogenic drop being investigated for GA
  - Recent study showed ineffective

Squalamine

- Eye drop derived from shark fin that has shown to have Anti-VEGF, Anti-PDGF, and Anti-bFGF properties
- Phase 11 trials
  - Lucentis PRN plus Squalamine bid had increased BCVA vs Lucentis alone
    - 48.3% vs. 21.2% had >15 letters gain
    - 10.4 mean gain vs. 6.3 gain
  - Primary endpoint of reduced frequency of injections not met
    - 6.2 vs. 6.4 over study
- Phase III enrolling
  - Looking at visual acuity gains over 6 mos

NRTI's

- HIV drugs, Nucleoside Reverse Transcription Inhibitors (NRTIs), found to block inflammation
- Stavudine and zodovudine prevented GA in a mouse study
  - Prevented GA progression in 5/6 mice administered orally daily vs. 0/6 control
  - Prevented GA in 8/9 mice received twice daily abdominal injections vs. 0/8 control
- Two additional trails under way: one oral and one intravitreal injection

Oral Fenretinide

- Oral medication being investigated for the treatment of GA
  - Theory is that the medication prevents delivery of retinol to the eye, a precursor of lipofuscin, which reduces retinol derived metabolites (A2E) that are toxic to the RPE and photoreceptors
- Has been studied for a few years
  - Given FDA fast track in 2009 after early studies

Oral Fenretinide: update

- 100 and 300 mg orally in 246 pts with GA at 30 sites in US for 2 years
- Mean reduction on o.33 mm^2 in yearly growth rate vs. placebo
  - 1.70 mm^2 /yr vs. 2.03 mm^2 per year
  - Reduced rate of conversion of CNVM by 45%
- Encouraging results further study indicated

Copaxone

- Copaxone (glatiramer acetate) is a immunomodulary substance which has been proven to be safe and effective in treating neurodegenerative disease, such as MS
- Phase II study will investigate if a weekly vaccination can stop the progression as well as conversion of dry to wet ARMD
  - New York Eye and Ear Infirmary

CNTF

- Ciliary neurotrophic factor (CNTF) intraocular implant, NT-501
  - Recent study of patients with GA
    - After 12 mos, 96.3% of high-dose group had stable vision vs. 75% with sham
    - Also showed increase in retinal thickness in treated group at 12 months

Stem Cells

- Stem cells: Transplantation of fetal RPE cells has been performed in pts with CNVM and GA
  - *American Journal of Ophthalmology*, August 2008
    - 10 patients (6 RP, 4 ARMD) with VA 20/200 or worse received RPE tissue
    - 7/10 had improved vision
  - Promising results, but many researchers feel widespread use may be decades away

AdaptDx

- Measures the rate of recovery of scotopic sensitivity after photo-bleaching as a diagnostic measure of AMD
- Not currently FDA approved for AMD
  - Approved as a dark adaptometer only
  - 18 clinical studies and trials
  - Over 1300 patients
  - Commercially available late 2012
- Decreased dark adaptation may precede clinical findings by as much as 4 years
- MacuLogix

Adapt DX

- Studies indicate dark adaptation is very sensitive for AMD diagnosis, more than other standard test
  - Dark adaptation 85% sensitivity
  - Snellen acuity 25%
  - Contrast sensitivity 25%
  - Photopic visual field 25%
  - Scotopic visual field 20%

Fundus Autofluorescence (FAF) Imaging

- Non-invasive technique which utilizes fluorescent properties of lipofuscin to study the health and viability of RPE/ photoreceptor complex
- In AMD, may help differentiate from similar entities
- FAF variation may precede retinal changes, and may be prognostic for those patients that will continue to develop vision loss

AREDS 2 home study

- 1520 pt with at least one large drusen and VA 20/60 better
  - 763 with home monitoring, 51 CNVM detected
  - 757 standard monitoring, 31 CNVM detected
    - 4 letters lost with device vs. 9 without
    - 94% had better than 2040 with device vs. 87% without