UPDATE ON AMD 2019

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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


JAMA

The JAMA Network

ORIGINAL CONTRIBUTION

ONLINE FIRST

Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration
The Age-Related Eye Disease Study 2 (AREDS2)
Randomized Clinical Trial

JAMA
The Journal of the American Medical Association

The Age-Related Eye Disease Study 2 (AREDS2) Research Group

Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration: The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial

Published online May 5, 2013

Available at www.jama.com

AREDS 2 Formulation

- Vitamin C-500 mg
- Vitamin E-400 iu
- Lutein 10 mg/Zeaxanthin 2 mg
- Zinc 80 mg
- Copper 2 mg

- NO beta Carotene
- NO 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

Lucentis (ranibizumab)

- Antibody fragment which blocks VEGF activity
  - Less specific than Macugen, so perhaps more efficacious
- Delivered by intravitreal injection
- Developed by Genentech
- 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

- 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

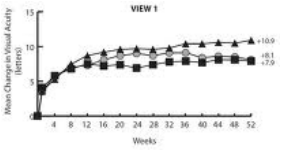
Avastin

- 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

Eylea (aflibicert)

View 1

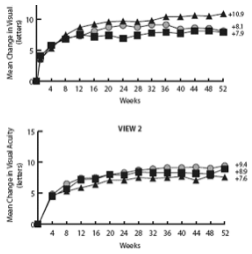
- 95% of pts receiving 2 mg q 2 mos achieved maintenance of vision vs. 94% with Lucentis monthly
- 7.9 letter mean improvement of vision (vs. 8.1 with Lucentis monthly)



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

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 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%)

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)

Seven-Up study

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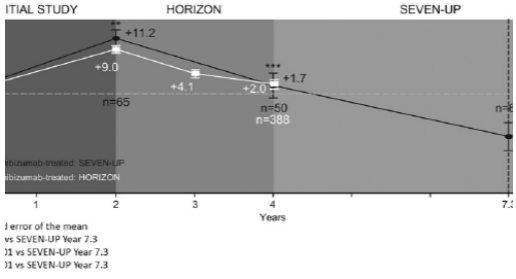
ɛn-Year Outcomes in Ranibizumab-Tre: ents in ANCHOR, MARINA, and RIZON

ulticenter Cohort Study (SEVEN-UP)

*ʼagha, MD, MPH,[1] Robert B. Bhisitkul, MD, PhD,[1] David S. Boyer, MD,[2] SriniVas R. Sadda, g, MD, PhD,[4] for the SEVEN-UP Study Group**

Seven-Up Study



CATT 5 yr Results

- ARVO 2016: 647 patients 328 Lucentis, 319 Avastin
- 5.5 years follow up on average
  - 25 total Visits or ≈4.55 /year
- 50% had VA > 20/40
- 20 % <20/200
- 10% 20/20
  - Loss of 3 letters from baseline
  - Loss of 11 letters from 2 year study endpoint
- Before VEGF: only 10% > 20/40

Potential Therapies

- Currently, there are ≈ 1404 studies evaluating AMD, both Wet and Dry
  - www.clinicaltrials.gov (March 2018)
    - More than:
      - glaucoma
      - dry eye
      - diabetic eye disease
- Exciting time to be involved, with many possible therapies that may prove useful for our AMD patients

FoVista (pegpleranib)

- Anti-PDGF agent
- Theory is that when used in conjunction with anti-VEGF agents, will have a better effect due to synergistic effect
- Ophthotech
  - Phase 1/ 2b studies promising

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
- Phase 3: Fovista 1.5 mg with anti-VEGF vs anti-VEGF monotherapy underway

FoVista: Update

- Dec 2016, Phase 3: 1248 pts with wet AMD
  - Fovista plus Lucentis: mean gain of 10.24 letters at 1 year
  - Lucentis only: mean gain of 10.01
  - Difference of 0.23 letters
  - 24.2% gained >20 letters with combo
  - 22.1% gained >20 letters with Lucentis alone
  - 12.1% lost 5 letters or more with combo
  - 11.2% lost 5 letters with Lucentis alone
  - 13.5% VA of 20/25 or better with combo
  - 13.9% VA of 20/25 or better with Lucentis

STOCK DECREASED 85% OVERNIGHT!!

Rinucumab

- Another PDGF from Regeneron
- CAPELLA study
  - Eylea plus rinucumab vs. Eylea alone for 12 weeks
  - Combo gained 5.8 letters, Eylea 7.5 letters
  - Failed to meet endpoint
  - Will continue study for one additional year

Lampalizumab

- Intravitreal Injection for GA (Roche)
- MAHALO Study
  - 20% reduction in GA lesion progression over 18 mos who monthly injections
  - Subset of pts with CFI injection had 44% reduction
- Phase III: 986 patients currently underway
- CHROMA, SPECTRI STUDIES
  - First results released September
  - Did not show a positive effect vs. no treatment on lesion size

Brolucizumab (RTH258)

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

Brolucizumab (RTH258)

- HARRIER and HAWK (phase 3 studies)
  - 6 or 3 mg of RTH258 vs. 2 mg Eylea in ≈1800 patients
  - Met primary endpoint at 48 weeks of non-inferiority in mean BCVA vs. Eylea
  - ≈55% remained on q 12 weeks injection schedule
  - Overall ocular and non-ocular adverse events were comparable to Eylea
  - "These results demonstrate RTH258 has potential to reduce injection burden while providing excellent visual outcomes"

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/RTH 258 Proof of concept

LADDER Study

- Genentech looking at a Rigid Port Delivery System (RPDS)
- Placed through a scleral incision
- Would release a constant influx of meds (Lucentis) rather than serial anti-VEGF injections
- Refillable every 4-6 mos
- Currently in Stage II

PAN-9080

- Pan Optica Biotech
- Topical anti-VEGF agent
- Phase 1/2 study
  - Positive response in 45-50% of 20 pts at 8 weeks
    - Decreased Vascular leakage
    - Change in lesion morphology
    - Change in Acuity
    - AE: SPK
- Also looking at role in DR and VO
- Data expected early 2019

Sunutib (G-102)

- Gray Burg Vision
- Encapsulated injectable sustained release formulation of SUTENT (Pfizer)
  - FDA approved 2006 for oral tx of advanced renal cell carcinoma, GI stromal tumors, and pancreatic non- endocrine tumors
- Has Anti-VEGF, Anti PDGF, stem cell growth factors and other modes of action
- Injected once per 6 mos
  - G-103: Yearly injection
- Animal studies currently, with human studies planned

OPT-302

- OPHTHEA: Australian Biotech company
- Blocks VEGF-C/D
- Phase 2b studies in US and Europe (351 pts)
  - Lucentis plus two doses of OPT-302 for WET AMD
    - Primary Endpoint: change in acuity at 24 weeks
    - Secondary Endpoints
      - Decreased retinal thickness
      - % pts with > 15 letter gain in acuity
      - Ocular and non-ocular adverse events

ICON-1

- Iconic Therapeutics
- Tissue factor TF inhibiter for WET AMD
  - Interferes with TFs ability to drive angiogenesis and inflammation
- EMERGE STUDY: 88 pts
  - Well tolerated
  - In conjunction with anti-VEGF
    - Reduced CNVM lesion size
    - Removed fluid from retina
- Starting Phase 2 studies

High Dose Atorvastatin

- 26 pts with AMD and large, multiple soft drusen
- High dose 80 mg atorvastatin (generic lipitor)
  - Typically 10-20 mg/day
- At 12 mos, 23 completed trail
  - Regression of drusen and acuity gain of 3.3 letters in 10/23
  - None progressed to wet AMD

Regression of Some High-risk Features of Age-related Macular Degeneration (AMD) in Patients Receiving Intensive Statin Treatment Demetrios G. Vavvas , Anthony B. Daniels , Zoi G. Kapsala, JeremyW. Goldfarb, Emmanuel Ganotakis,John I. Loewenstein, Lucy H. Young, Evangelos S. Gragoudas, Dean Eliott, Ivana K. Kim,Miltiadis K. Tsilimbaris , JoanW. Miller

Stem Cells

Table 1. Active Stem Cell Investigations in Retinal Disease

Investigational Product	Cell Type	Sponsor	Administration Route	Number of Cells	Patient Population	Clinical Trials	Status	Length	# Subjects
MA09-hRPE	hESC-derived RPE	Ocata Therapeutics	Subretinal transplantation	50K - 200K	Dry AMD with GA	Phase I/II, NCT01344993	Ongoing, Not recr.	12 months	16
MA09-hRPE	hESC-derived RPE	Ocata Therapeutics	Subretinal transplantation	50K - 200K	Stargardt's disease	Phase I/II, NCT01345006	Ongoing, Not recr.	12 months	16
MA09-hRPE	hESC-derived RPE	UCLA	Subretinal transplantation	Unknown	Myopic macular degeneration	Phase I/II, NCT02122159	Not yet recruiting	12 months	Unknown
HuCNS-SC	Adult neural SC	StemCells Inc.	Subretinal transplantation	200K - 1M	Dry AMD with GA	Phase I/II, NCT01632527	Closed	12 months	15
CNTO 2476	UCSC	Janssen R&D	Subretinal transplantation	60K - 300K	Dry AMD with GA	Phase I, IIa NCT01226628	Closed	12 months	24
PF-05206388	hESC-derived RPE	Pfizer	Subretinal transplantation	17 mm^2 sheet	Wet AMD	Phase I, NCT01691261	Not yet recruiting	12 months	
	BM-derived SC	Univ. San Paulo	Intravitreal injection	1M	Dry AMD, wet AMD and Stargardt's	Phase I/II, NCT01518127	Enrolling	12 months	10

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
    - AAV2.sFLT01
  - Avalanche Biotechnologies
    - AVA-101
  - Oxford BioMedica
    - RetinoStat
  - For Sight Labs
  - NeuroTech

Brimonidine®

- Glaucoma medication by Allergan
- Long suspected to have neuro-protective properties
  - New studies point at retinal neuroprotection in animals
- BEACON STUDY
  - Evaluating an intravitreal insert for GA
  - 2016 AAO subspecialty day
    - 132ug: 19% reduced rate of regression
    - 265ug: 28%

APL-2

- Apellis Pharmaceuticals
- Intravitreal Complement factor C inhibitor for GA
- FILLY Trial: Phase 2 showed decreased rate of lesion progression over 12 mos in monthly and every other month administration
  - Monthly 26%
  - Ever other: 20%
- Phase 3 to start soon

MacuLogix's AdaptDx

- Dark adaptation is a sensitive marker for early AMD
- The AdaptDx measures dark adaptation
- A rapid test of dark adaptation using the AdaptDx has been found to have a 90% sensitivity for detecting dark adaptation impairment associated with AMD
- Decreased dark adaptation may precede clinical findings of AMD
- Dark adaptation is more sensitive than other tests such as Snellen acuity, contrast sensitivity, or visual fields which are about 25% sensitive.

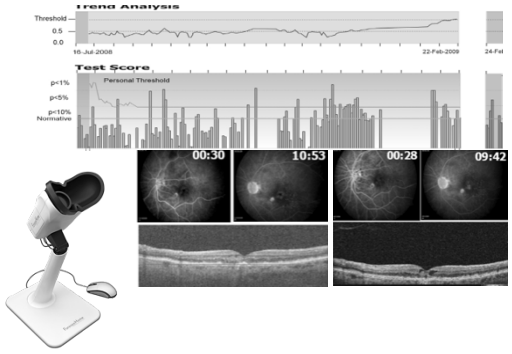
AdaptDx Study at VA

- Tested whether the AdaptDx could detect AMD in a typical VA clinical setting
- Rapid test run on 19 AMD patients (AREDS stage: 1 to 3)
- 18 of 19 patients failed to dark adapt before the maximum test time of 6.5 minutes. The diagnostic test sensitivity was 94.7%
- The AdaptDx exhibited similar sensitivity in a working VA clinic compared with a multi-site clinical study
- Next step is to use the AdaptDx to find patients with undiagnosed AMD or subclinical AMD

AdaptDx Advantages

- No preadaptation required
- Protocols as rapid as 5 minutes
- Low patient burden
- Easy to operate
- CPT 92284 ($64 avg.)
- FDA 510K cleared (K100954)

Foresee Home



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

My Vision Track (mVT®)

- An app to detect early vision problems in patients with AMD and DM, leading to sooner assessments and better vision retention
- FDA cleared
- 98% effective rate in detecting changes

CONCLUSION

- Exciting time to be interested in AMD
- New treatments on horizon that may be beneficial to our patients
- New advances in diagnosis and detection are paramount
  - On study determined 25% of pts deemed normal on dilated retinal exam by eye care physician had characteristics of AMD on photographic review