# Landmark Studies from the NEI

## Current Treatments and Future Horizons in Ocular Disease

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## Mark Dunbar: Disclosure

- Optometry Advisory Board for:
  - Allergan
  - Carl Zeiss Meditec
  - ArticDx
  - Sucampo

Mark Dunbar does not own stock in any of the above companies

## Historical Perspective of the NEI

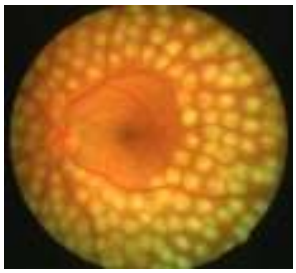
- 1968 President Lyndon Johnson signed into legislation establishing National Eye Institute (NEI) as part of the Federal Government's National Institute of Health (NIH)
- Vision scientists gain financial recourses to have world parity and finding the answers to challenging questions in eye disease

## Historical Perspective of the NEI

- Is light photocoagulation safe and effective in the treatment of diabetic retinopathy?
- 1972 NEI launched the Diabetic Retinopathy Study (DRS)
- 1st large collaborative controlled clinical trial in the history of ophthalmology

## Historical Perspective

- By 4 yrs study provided established a valid scientific basis for performing laser photocoagulation in diabetic patients that are at risk of losing vision
- Over 55 studies have been completed in the major areas of ocular disease



## NEI Studies

- Well designed
- Find answers to practical problems
- Appropriate number of patients necessary to arrive at a conclusion
- Control group
- Conclusions have a scientific basis

## Evidence Based Medicine

Definition:

**The integration of the best research evidence with clinical expertise and patient wishes to arrive at the appropriate management**

**Put another way:**

**Making clinical decisions based on valid evidence rather than intuition, hearsay, or peer practice.**

## From the NEI
## The Most Recent Data of Vision Loss from Eye Disease

Arch of Ophthalmology April 2004

- Blindness or Low Vision affects 3.3 million > 40 yo
  - Or 1 in 28 will be blind or need low vision care
- By year 2020 -> 5.5 million
- Those > 80 yo (8% of the population) account for 69% of blindness

## From the NEI
## The Most Recent Data of Vision Loss from Eye Disease

Arch of Ophthalmology April 2004

Leading cause in blindness:

- White population: AMD (54% of blindness)
- African Americans: Glaucoma and Cataracts
  - GL is 3X as common in African Americans vs white
- Hispanics: Glaucoma
  - Rises rapidly in Hispanics > 65 yo
- Diabetes: 1 in 12 > 40 yo will have vision threatening DR

## Eye Disease Prevalence and Projections

Arch of Ophthalmology April 2004

| | Current Estimates (Millions) | 2020 Projections |
|---|---|---|
| Advanced AMD | 1.8* | 2.9 |
| Glaucoma | 2.2 | 3.3 |
| Diabetic Ret | 4.1 | 7.2 |
| Cataract | 20.5 | 30.1 |

*Another 7.3 million are at substantial risk for vision loss from AMD

## Glaucoma

- Leading cause of blindness in US and other industrialized countries
- 3 million people in US have glaucoma
  - 50% are unaware they have glaucoma
- 80,000 people legally blind from glaucoma
- # 1 cause of blindness in African Americans
  - Baltimore Eye Survey, the age-adjusted prevalence rates of POAG were 4 to 5 X > in African Americans than among white individuals
- #1 cause of blindness in the Hispanic population

## Estimates of Future Glaucoma

- Prevalence models projections based on populations-based studies
- 2010: 60.5 million will have OAG
  - 4.5 million with OAG, 3.9 million with ACG will be blind in both eyes
- 2020: 79.6 million
  - 47% will be Asian
  - 87% with ACG will be Asian

Quigley et al, BJO. 2006; 90:262-267

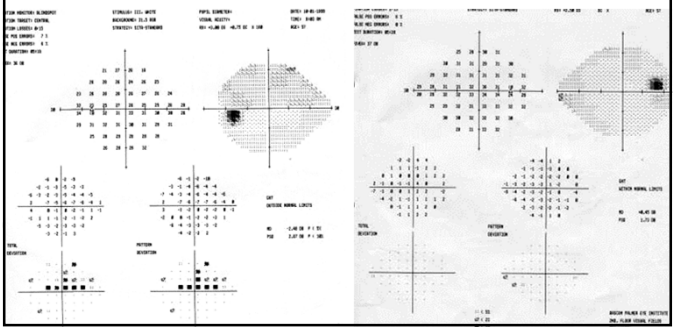
## IOP and Glaucoma

- Lowering IOP < rate of glaucomatous ON damage
  - But how low does IOP need to be?
- Every method of lowering IOP causes side effects, cost money, and involves risks
- Benefit of lowering IOP should out weigh the risks and cost of Tx

## Luisa: Hispanic Female Initial Presentation

- Presented for routine exam
- VA: 20/20 OU
- TA: 26 OD; 27 OS
- Gonioscopy – CBB 360 OU, No PAS
- ON: 0.55 – 0.6 OU Inferior notch

## Louisa Hisp Female Initial Presentation



## Luisa

- What should her initial management be?
  - What is the basis for starting medical therapy?
  - Is there any argument that could be made for not treating?
- If we don't treat her – will she go blind?
  - At what rate will she loose visual field?
- What is the risk of blindness?
- How low does the pressure need to go?

## Early Management of Glaucoma Treatment Study (EMGT)

- Does early treatment alter the natural course of the disease in POAG?
- NEI supported clinical trial performed in Sweden
- Early POAG, PDG, PXF
- Randomized:
  - ALT vs. Betaxalol vs. Careful Observation

## Early Manifest Glaucoma Trial (EMGT)

Goals:

- Evaluate the effectiveness of reducing IOP in early OAG
- Explore factors that may influence glaucoma progression
- Describe the natural history of newly detected glaucoma

Leske MC, et al. Early Manifest Glaucoma Trial. Design and baseline data. *Ophthalmology* 1999;106:2144-2153.

## EMGT

- 1st randomized, controlled, clinical trial to evaluate the effect of lowering IOP on progression of newly detected OAG
- Compared progression in initially Tx eyes vs. untreated patients
- Will allow quantification effect of immediate IOP-lowering on progression
- Identify factors related to progression
- Study natural history

## EMGT

- Ages 50-80 yo
- >250 patients enrolled
- Followed for a minimum of 4 yrs
- IOP 25-35 Randomized
- IOP > 35 on 2 visits decision regarding Tx
- Progression based on VF and optic nerve status

## EMGT

- 255 OAG patients (POAG, NTG, PXF)
- 129 randomized to 360° ALT & betaxolol
- 126 randomized to observation
- Mean age 68 years old
- 66% women
- Mean baseline IOP 20.6

## EMGT

- Follow up visit with VF q 3 mos
  - disc photos q 6 mos
- Progression monitored with
  - Full threshold VF with Glaucoma Change Probability (using pattern deviation values)
  - Flicker chronoscopy of nerve photos, side by side comparison for suspected change

## EMGT

**Endpoints:**

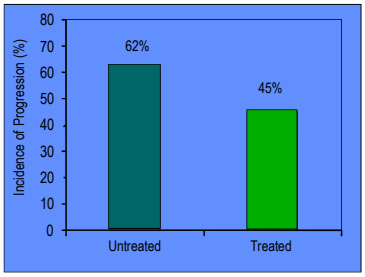
- VF progression (3 consecutive HVFs)
- ON progression (2 consecutive sets of stereo disc photos)

## EMGT Results

- Median f/u 6 years
- Avg decrease IOP in Tx'd group 25% or 5.1mmHg
- 53% progressed -> 47% did not progress
  - 45% (58/129) Tx'd v. 62% (78/126) control
  - Longer time to progression in the tx'd group
    - Median time to progression 18 mos longer in tx'd group

## EMGT: Early Treatment Reduces Glaucoma Progression

- 255 patients with newly detected glaucoma
- No target IOP set
  - Average IOP drop 25% (range 0-29%) with Tx
- Progression in 45% of treated vs 62% of untreated patients ($P = .007$)
- Results show that treatment delays disease progression




## EMGT

| | Treatment Group | Control Group |
|---|---|---|
| Baseline IOP | 20.6 | 20.9 |
| IOP at 3 month follow-up | 15.5 | 20.8 |
| Percentile change in IOP | 25% | 0.5% |

## EGMT

| | Treatment Group | Control Group |
|---|---|---|
| Progression | 58 (45%) | 78 (62%) |
| Based on VF | 53 (41%) | 64 (51%) |
| Based on ON | 1 (1%) | 0 (0%) |
| Based on VF + ON | 4 (3%) | 14 11%). |

Heijl A, et al. Reduction of intraocular pressure and glaucoma progression. Results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2002;120:1268-1279

## EMGT

**Baseline factors that predicted progression on a multivariate analysis:**

- Higher IOP
- Exfoliation
- Worse MD
- Older age
- Frequent disc hemorrhages

Leske MC, et al. Factors for glaucoma progression and the effect of treatment. The Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2003;121:48-56.

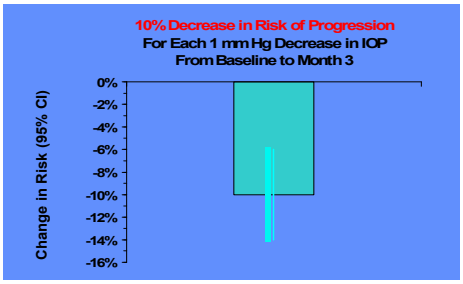
## Lessons from the EMGT

- Treatment works…
- Average rate of progression was 2.3 dB over 10 yrs
- Rate of progression was decreased by 10% for every 1 mmHg reduction of IOP
- NonTx Group: 1/3 of pts 6 yrs out still have no progression

## Recommendations for Management from the EMGT

- Newly Dx pts should be followed often
- Take more VF's early –establish rate of progression – up to 7 VF over 2 yrs
- Pts with rapid progression should be vigorously treated
- Tx should be tailored for each patient

## EMGT: Every mm Hg of IOP Lowering Matters




Leske et al. *Arch Ophthalmol.* 2003.

## IOP Parameters and Risk of Progression

- Mean IOP in study populations best studied
  - Lower mean IOP = lower risk of progression
- For individual patients, risk is reduced with each additional 1 mm Hg reduction in IOP
- Important new IOP parameters related to risk of progression in individual patients
  - Consistent achievement of target IOP
  - IOP variation over the long term
  - Daily fluctuation in IOP

## Lessons from the EMGT

- Average age of defect discovered -> 72 yo
  - Most pts at this age will not go blind or get any disability from blindness
- Average 70 yo patient diagnosed with glaucoma is expected to live 12 years
- He/she will loose ~ 4.2 dB during his remaining lifetime
- This patient will likely not "get in trouble" unless he starts with MD of $\leq$ 10 dB

## Lessons from the EMGT

### Low Risk Patients

- Patients with early stage disease…and
- Low IOP's
  - Is at low risk for rapid progression
  - Tx affect is rather small
- May leave room for recommending close follow up with no treatment
- Elderly w/ unilateral Dz also considered low risk

## Luisa: POAG

We know that treatment is beneficial vs. no treatment

- Slow the rate of progression

- How low does IOP need to be?
- If our initial treatment fails – what should be the 2nd option?

## Advanced Glaucoma Intervention Study (AGIS)

- To assess long-range outcome in sequence of interventions in Trab vs ALT in eyes who have failed initial med therapy
  - Studying being done b/c varying degrees of success with either procedure.
- Eyes randomized:
  - Trab followed by ALT followed by trab (TAT)
  - ALT - trab - 2nd trab (ATT)
    - May use antifibrolytic agents on 2nd surgery

## Advanced Glaucoma Intervention Study (AGIS)

- Recruitment began 1988, closed in 1992
- 789eyes (591 pts) with "advanced" glaucoma
- Minimum 5 yr follow up
- Primary outcome (APDVA, APDVF, APDV)
  - Average % with decrease visual acuity, visual field, vision
- Subsidiary outcome: Is there a racial difference b/w treatment regiments?

## AGIS: Results Demographics:

- 332 black (451 eyes) vs 249 white (325 eyes)
- 57% black, 54% female
- Blacks were: younger, more HTN, more diabetes, worse VF on enrollment, more hyperopes, less likely to have notching out to rim, fewer Drance hemes, on more meds upon enrollment (2.8 vs 2.5)

Ophth July 1998. AGIS 3. Baseline Characteristics B&W

## AGIS: Results

- Blacks had better results ATT sequence
- Whites (woltc) had better results TAT sequence
- Decrease in IOP > in TAT group (both B&W)
- ATT group had higher failure rate of 1st intervention

Ophth July 1998. AGIS 4. Comparison of Treatment Outcomes with in Races

## AGIS Results

Number of prescribed glaucoma meds

- Average # decreased sharply for both B&W in Trabec group
  - Trab: 2.5 meds at baseline vs 0.5 @ 3 months
  - ALT: 2.5 meds at baseline to 2.0-2.5 @ 3 mo
- By 7 yrs, the difference in meds is 0.5 b/w 2 groups
- Quality of life issues not addressed in AGIS

## AGIS: General Considerations

- Results b/w 2 groups (TAT vs ATT) were equal until race was considered
  - Blacks: Greater advantage for ALT blacks
  - White: Greater advantage for Trab after 4 yrs
- Results are based on groups as a whole and not individual patients
- Stage of disease was not considered
  - "Adv Glaucoma" = on max med therapy
- Results may be different if treatment was based on the need to aggressively lower target IOP in any given patient

Ophth July 1998. AGIS 4. Comparison of Treatment Outcomes with in Races

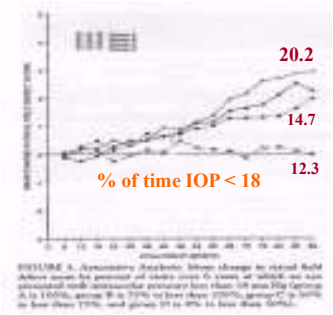
## Glaucoma and Pressure What is the relationship?

- How much of glaucoma damage is pressure dependent?
- How effective is pressure lowering in preventing further field loss?
- How low does the pressure have to be to achieve the maximum benefit?

## AGIS: IOP and Field Loss

- 789 eyes followed for 6-11 years
- 4 analysis groups based on how often IOP < 18
  - 100% visits
  - 75- 99%
  - 50-74%
  - < 50% of visits

Report # 7 AJO Oct 2000

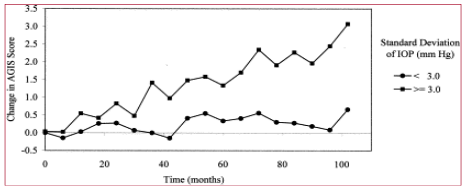



## AGIS: IOP and Field Loss Implications??

- Results specific for patients with POAG
  - Do not apply to OHT or NTG
- Patients with moderate/severe VF Loss
- Strive to achieve IOP in the "low teens" range
  - Likely to require multiple meds
  - Laser and/or surgery may be required

Report # 7 AJO Oct 2000

## AGIS: Patients With Small IOP Variation Had Stable Fields




- Eyes with variation < 3 mm Hg: no average progression
- Eyes with variation ≥ 3 mm Hg: on average, significant progression

Nouri-Mahdavi et al. *Ophthalmology.* 2004.

## Back to Luisa…

**Would surgery be reasonable consideration as a 1st line of treatment?**

## Chop or Drop

Several studies have questioned traditional beliefs regarding treatment:

"Are we in fact harming our patients by delaying surgery until there is evidence of further field loss, and/or deterioration while utilizing medical and laser regimens."

Survey of Ophthalmology 1993

- Does medical therapy/ALT provide as good longterm control of IOP as surgery in preventing continued field loss?
- Is medical therapy truly benign?
- Is the overall "quality of life" better with standard medical therapy or with surgical intervention?

## Collaborative Initial Glaucoma Treatment Study (CIGTS)

- Purpose: To compare the long-term effect of treating newly diagnosed POAG with standard medical vs. filtration surgery
- 607 pts randomized b/w Oct 93 – April 97
- Follow-up through 4 years and partially completed through 5 years
- Both groups had substantial/sustained ↓ in IOP

## CIGTS and IOP

- Surgery 2-3 less than Medical
- Medicine group averaged 17 to 18
- Surgery group averaged 14 to 15

Lichter PR, et al Ophthalmology 2001 Nov;108(11):1943-53

## CIGTS: Visual Fields and Cataract

- VF loss did not differ by Tx
  - Surgery group had > VF loss and > VA loss in 1st 3 yrs, but equal by yrs 4-5
- Rate of cataract development greater surgery group

Lichter PR, et al Ophthalmology 2001 Nov;108(11):1943-53

## CIGTS: Quality of Life

- Both groups satisfied
  - Surgery: more local eye symptoms, irritation
    - Most disappeared by yrs 4-5
  - Medical: variety of systemic symptoms, but not consistent over time
    - Clearly different from surgery Sx

Janz NK, Wren PA Ophthalmology 2001 Nov;108(11):1954-65

## CIGTS: Conclusion

- Both surgery and medicine as initial Tx result in the same VF outcome at 5 yrs
- Investigators do not recommend changes to current approaches of management
- Longer follow up is needed as this is a chronic disease
  - 4-5 yrs is not adequate time to draw conclusions

## CIGTS Bottom Line

- At 5 yrs, no difference between surgery and medicine for control of IOP
- The study legitimized surgery as a primary procedure for treating newly diagnosed GL
  - When all was said and done – surgery resulted in lower IOP vs Medicine
  - Safe
  - Overall in the long-term – may prove be better

## Jane: 47 yo WF 5/27

- "Glaucoma Suspect" (No records)
- Unremarkable medical Hx
- TA: 20/20 OU
- TA: 32 OD 29 OS
- Dics: 0.45 OD 0.5 OS
- VF:
- How would you manage this patient?

## Questions?

- Should we treat her?
- What is her risk of developing glaucoma:
  - If her cornea is 600 µ?
  - If her cornea is 490 µ?
- Are you influenced by race – white vs. AA

## Ocular Hypertension Treatment Study (OHTS)

- Long-term randomized, multicentered controlled, clinical trial
- 1500 OHT pts with moderate risk for POAG randomized
  - Observation vs stepped medical therapy
- 5 yr minimum follow up
- Pts seen 2X/yr for IOP ck and HVF

## Ocular Hypertension Treatment Study (OHTS)

- 30-40 clinical centers
- Each center randomized minimum of 50 pts
- Men and women 40-80 yo
- IOP
  - $\geq$ 24, $\leq$ 32 in 1 eye
  - $\geq$ 21, $\leq$ 32 in the fellow eye

## OHTS
*Arch Ophthalmol*
June 2002;120:701-713

- 1636 participants randomized, followed 60 mo
  - Observation vs Treatment
- Goal: Reduce IOP 20% or IOP $\leq$ 24
  - Treatment: reduction 22.5% $\pm$ 9.9%
  - Observation: reduction 4.0 $\pm$ 11.6%
- Outcome: reproducible visual field defect or Reproducible optic disc deterioration

## OHTS Results
*Arch Ophthalmol*ogy
June 2002;120:701-713

- Treatment reduced the chance of developing glaucoma by $\geq$ 50%
- The chance of developing POAG in 5 yrs:
  - Observation group: 9.5%
  - Treatment group: 4.4%
- Conclusion: Meds are effective in delaying or preventing the onset of POAG

## OHTS
### *Arch Ophthalmol*
### June 2002;120:701-713

- 55% of POAG endpoints involved ON changes in the absence of VF endpoint
- EMGT: < 10% progressed based on ON
  - > 90% progressed based on VF

## Corneal Thickness and OHT
Arch Ophthal June 2002:;120:714-720

- Corneal thickness was a strong predictive factor
- Corneal thickness of < 555 µ had a 3X greater risk for developing POAG vs pts with thickness > 588 µ
  - African Americans had 23.5 µ thinner corneas than other races – closer to normal
  - Other races had thicker corneas than normal

## Risk Factors POAG
Arch Ophthal June 2002:;120:714-720

- Thin corneas
- Age
- Cup-disc ratio
- IOP
- Race – but African Americans had thinner corneas and greater vertical C/D ratios
  - Sig in Univariate analyses (59% greater risk), not sig in multivariate analysis
- Reduced PSD at baseline (need multiple VF's)

## Which are NOT Risk Factors POAG?

- Family Hx of glaucoma not a risk factor
- Myopia – Not a risk factor
- Diabetes – "Protective" against POAG
- Migraine
- CVA
- HTN
- Low blood pressure

## OHT: 5 Yr Risk for POAG

- Baseline IOP of 25.75 mmHg
  - Ave Corneal thickness < 556 µ: 36% Risk
  - Corneal thickness 565 to 588 µ: 13%
- Cup-Disc ratio > 0.3
  - Ave Corneal thickness < 556 µ: 24%
  - Corneal thickness 565 to 588 µ: 16%

## POAG Risk Over 5 Years by Central Corneal Thickness and Baseline IOP in Observation Group

## POAG Risk Over 5 Years by Corneal Thickness and Baseline Vertical C/D Ratio in Observation Group




## OHTS
### *Arch Ophthalmol*
### June 2002;120:701-713

- Of Note: Because GL is the leading cause of blindness in African Americans, recruitment was extended to ensure that 25% was AA in origin -> 400 AA enrolled
- This is the 1st study to recruit large #'s of AA to look at the benefit of IOP lowering eye drops

## Latest Update from OHTS Embargoed Release 6/14/2004

Archives of Ophthalmol; June 2004

### African American Population

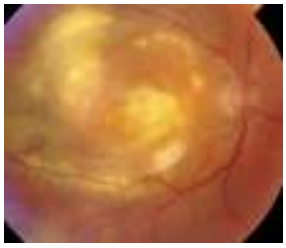
- Treatment lowered risk of glaucoma by almost 50%
  - Treated group: 8.4% developed POAG
  - Untreated group: 16.1% developed POAG

## Factors Result in > Risk of POAG in AA Population

- Genetic susceptibility to POAG
- Higher prevalence of co-morbidity
  - Such as cardiovascular disease
- Earlier onset of POAG
- Later detection of POAG
- Economic and social barriers to treatment

## Age-related Macular Degeneration (AMD)

- Degenerative disorder that affects the macula
- Leading cause of legal blindness in people > 65 yo
- 90% of vision loss is 2° to CNV
  - Develops in 1.2% of adults 43-86 yo (Wisconson Beaver Dam Eye Study)



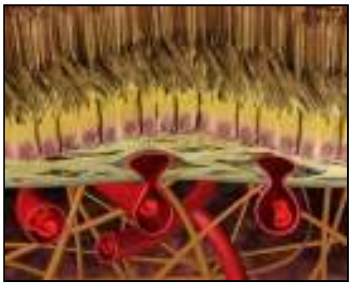
## NEI News Release March 2005

Gene Found to Increase Risk of AMD

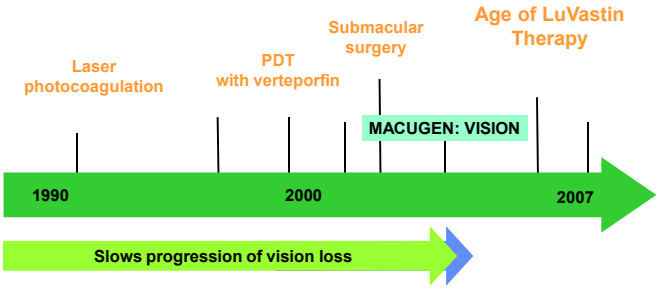
- 4 independent research teams (including NEI) discovered a gene that is "strongly associated" with the development of AMD
- Gene is called Compliment Factor H
- CFH gene produces a protein that helps regulate inflammation in part of the immune system that attacks diseased and damaged cells
- Those whose genetic makeup includes a variant of the CFH gene are 7.4 X more likely to develop AMD

## Choroidal Neovascularization (CNV)

- Growth of new blood vessels originating from the choroid
- Growth under the sub-RPE or subretinal space



## Therapy for Neovascular AMD




## Macular Photocoagulation Study (MPS)

- Randomized controlled clinical trial evaluating effectiveness of laser on CNV's
- 3 Disease Process: AMD, POHS, Idiopathic
- Extrafoveal (200 to 25000 u)
- Juxtafoveal (1-199 u)
- Subfoveal (CNVM extends into the FAZ)

## MPS Results

- Laser Tx was effective in reducing/delaying central VA loss from CNV
- Significant VA loss results even with successful Tx
- Up to 50 % recurrence rate of CNV post Tx
- Most patients (w CNV's) are not candidates for laser
  - CNVM too large
  - CNVM poorly defined by FA (occult - 75%)

## Laser Photocoagulation

- Benefits only a small minority of patients
- Only for classic, well defined CNV
- Destroys normal retina tissues
- Creates a scotoma
- Is associated with a unacceptably high CNV persistence and recurrence rate

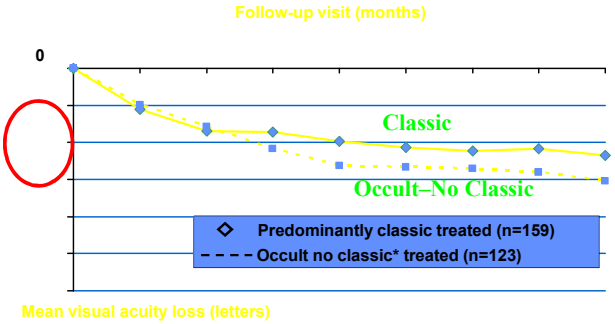
## Photodynamic Therapy (PDT)

- Photosensitizing dye (Verteporfin)
- Slow infusion into the arm
- Drug activated by nonthermal laser light – 689 nm
- Photochemical reaction results
- Leads to platelet activation -> thrombosis and occlusion of CNV

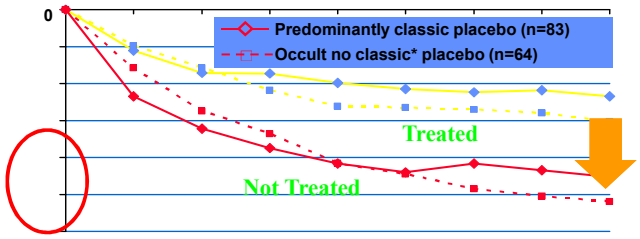
## How Effective is PDT?

- From the TAP study, successfully treated patients averaged 20/160-2 at 24 months
- Patients often need multiple treatments.
  - 5.6 treatments (TAP study) and 4.9 treatments (VIP study) over 24 months

## With Treatment, Average Outcome is a Loss of Vision…




## … But Less Loss Than With No Treatment




## Vascular Endothelial Growth Factor (VEGF)

- Multifunctional protein
- Angiogenic and vascular permeability properties
- Mediator of developmental and pathological intraocular vascularization
- May be a major cause of vascular leakage in diabetes

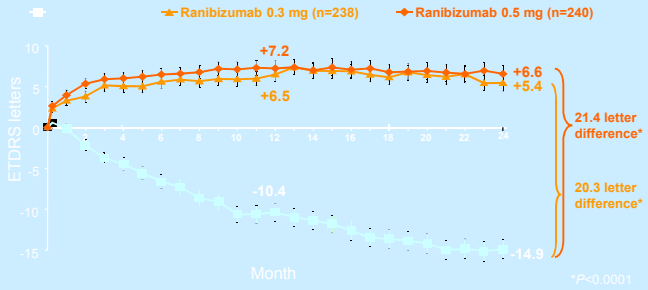
## Lucentis (Genentech)

- Recombinant humanized antibody "fragment" binds to VEGF
  - Targets a different isoform of VEGF than Macugen
- Prevents VEGF from interacting with the VEGF receptor on the surface of endo cell
- Injected into vitreous
- Transparent jelly-like substance fills the vitreous cavity
  - Rapidly passes through the retina and into the subretinal space to the RPE (1hr)

## Lucentis Phase III Clinical Trials

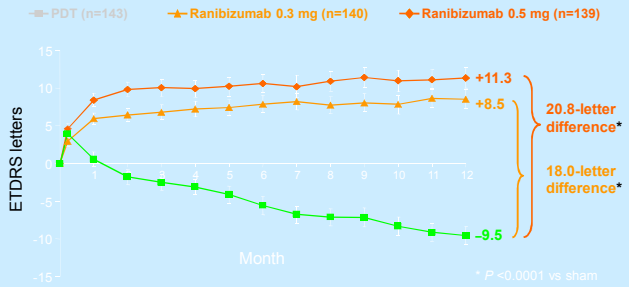
- MARINA trial
  - AMD pts with subfoveal minimally classic or occult-only CNV tx with monthly injections 300g or 500g vs. sham
  - Followed for 24 months
- ANCHOR trial
  - Predominantly classic CNV to receive monthly injections of 300g or 500g vs. PDT
  - Evaluated q 3 mo then receive PDT vs. placebo
  - 1° endpoint is lose of at least 15 letters of VA

## Secondary Endpoint:
### Mean Change in Visual Acuity Over Time




Note: Vertical bars are ± one standard error of the mean.

## Secondary Endpoint:
### Mean Change in Visual Acuity Over Time




Note: Vertical bars are ± one standard error of the mean.

## Lucentis Phase III Results: MARINA and ANCHOR Trial

- 95 % treated eyes maintained vs. 60% control group at 12 and 24 months
- 40% of treated patient had 20/40 VA vs. improvement in VA
- 90% treated with Lucentis at year two maintained or improved vision compared to 53% in the control arm

## Avastin® (bevacizumab, Genentech Inc.)

First anti-VEGF therapy approved by the FDA

Avastin®
Bevacizumab
MW 150 kD


FDA approved as a first line therapy for metastatic colorectal cancer on February 26, 2004

## Why consider Avastin in ophthalmology?

- Patients losing vision on current therapies
- Lucentis and Avastin have nearly identical binding properties
  - Functionally the same molecule
- Avastin is available off-label
- Intravitreal Lucentis improves vision but not yet FDA approved

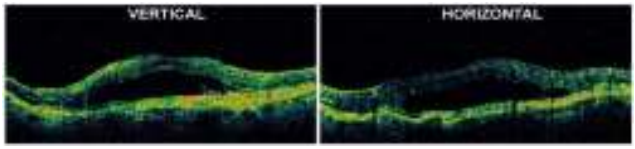
## Intravitreal Avastin

- First patient injected May 2005
- Two papers published in July 2005
- Number of eye-related Avastin PubMed citations:
  - 2006: 82
  - October 2007: at least 120
- Number of abstracts at ARVO 2007: 222

## First AMD case reported in July 2005

63 y.o. woman s/p PDT + Kenalog X 2 for predominantly classic CNV due to AMD.

Now 6 wks s/p Macugen #2 with drop in VA from 20/200 to 20/400




## Intravitreal Avastin

- Appears non-toxic in cell culture and animal studies
- Appears safe and effective in short-term retrospective and prospective studies
  - Highly reproducible!
- Optimal dose and dosing interval is unknown

## Lucentis vs. Avastin (Genentech vs Genentech)

COST

- Lucentis -> $ 2500 - $3,000 per injection
  - $3300 per mg
- Avastin -> $ 5.50
  - 1.25 mg costs $6.88
- If dispensed by a licensed pharmacist directly from the vial to the syringe, cost rises to between $17 and $50 a syringe

## Lucentis vs. Avastin

### Is one drug better than the other?

No randomized controlled clinical trials have compared the safety and efficacy of Lucentis to Avastin

## Lucentis vs. Avastin

- Large prospective comparative clinical trials comparing ranibizumab with bevacizumab will begin in 2007:
  - (US/NEI) Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Daniel Martin, MD
  - (UK/NHS R&D) A randomised controlled trial of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN) Trial Usha Chakravarthy, MD

## Avastin vs. Lucentis

### Treatment of Choice?

- NEI/NIH to sponsor head-to-head trial
- Complications of Age-Related Macular Degeneration Treatment Trial (CATT)
- 1200 patients randomized
  - Lucentis with 4 week dosing
  - Avastin with 4 week dosing
  - Lucentis with variable dosing
  - Avastin with variable dosing
- Followed for 2 yrs, and 4 yrs to complete

## Lifestyle Changes to Prevent AMD

- Does making lifestyle changes prevent the development of AMD?
- Justifiable in other diseases
  - Diabetes, hypertension and heart disease
- Can it affect the development of AMD?
- What is the role of nutrition in AMD?
  - What about antioxidents and other vitamins and supplements on AMD?

## What is Your Basis for Prescribing Vitamin Supplements to Prevent Wet AMD?

- I recommend supplements to all patients…
  - Over a certain age
- I recommend only if there are drusen
  - Even if only 1 drusen
- I recommend only if there is a lot of drusen
- I don't recommend Vitamin supplements

## What is the role of Anti-oxidants on AMD ?

- What are anti-oxidents?
  - Beta-carotene, Vit A, E, C and Selenium
- Are Beta-carotene levels inversely related to AMD?
  - Visible and UV light damage the retina via production of "superoxide" radicals
  - Antioxidants protect against oxidative damage -> act as scavengers

## Age Related Eye Disease Study (AREDS)

- Purpose: Assess clinical course, prognosis, and risk factors of ARMD and Cataract
- To evaluate (randomized clinical trial) the effects of pharmacologic doses of:
  - Antioxidents and Zinc on the progression of ARMD
  - Antioxidents on the development and progression of lens opacities

## AREDS

- 11 Center double-masked controlled clinical trial
- Recruitment began Nov 1992, ended Jan 98
- 90% followed for a minimum of 5 years
- 3640 people enrolled and categorized

- Extensive small drusen
- Intermediate drusen
- Large drusen
- Noncentral geographic atrophy
- Pigment epithelial abnormalities
- Advanced AMD or vision loss in 1 eye

## AREDS

4757 Pts (55-80 yrs of Age) from 11 Centers Randomized 3640 Studied

- 1117 excluded because no AMD

- Zinc alone
- Antioxidants alone
- Combination of antioxidants and zinc
- Placebo

## The Nutrients

- Vit C 500 mg
- Vit E 400 international units
- Beta-carotene 15 mg
- Zinc 80 mg (Zinc oxide)

- 2/3 chose to take an additional multi-vit

## AREDS Results

Arch of Ophthalmol Oct 2001

- "Eyes at high risk of developing Advanced AMD lowered their risk by 25% when treated with high dose combination Vit C, Vit E, beta-carotine and zinc"
- Combination of antioxidants and zinc had a 25% lower risk of developing "Advanced AMD" in eyes that were at "high risk"
  - Intermediate and advanced AMD group in one eye but not the other

## AREDS Results

Arch of Ophthalmol Oct 2001

**Antioxidants + Zinc**

- Reduced risk of developing advanced AMD by 25%
- Reduced risk of vision loss by 19%

**Zinc Alone**

- Reduced risk of developing advanced AMD by 21%
- Reduced risk of vision loss by 11%

## AREDS Results

Arch of Ophthalmol Oct 2001

**Antioxidant**

- Reduced risk of developing advanced AMD by 17%
- Reduced risk of vision loss by 10%

## AREDS Results Arch of

Ophthalmol Oct 2001

### Side effects

- 7.5 % (vs 5%) had UTI that required hospitalization
- Zinc group had slightly higher rate of anemia
- Beta-carotene group noted yellowing of the skin
  - May increase risk of lung Ca in smokers

## The Age-Related Eye Disease Study 2 (AREDS2)

- A Multi-Center, Randomized Trial of Lutein, Zeaxanthin, and Omega-3 Long-Chain Polyunsaturated Fatty Acids (Docosahexaenoic Acid [DHA] and Eicosapentaenoic Acid [EPA]) in Age-Related Macular Degeneration

# AREDS 2

**Protocol Number: 07-EI-0025**

- 4,000 pts ages 50 to 85 who are at high risk of having advanced age-related macular degeneration randomized
- Pts will be randomized to: placebos (sugar pills) vs. standard AREDS formulation
  - (vit C, vit E, beta-carotene, zinc oxide, and copper)
  - Pts who have smoked within the past year will not receive the standard formulation b/c beta-carotene

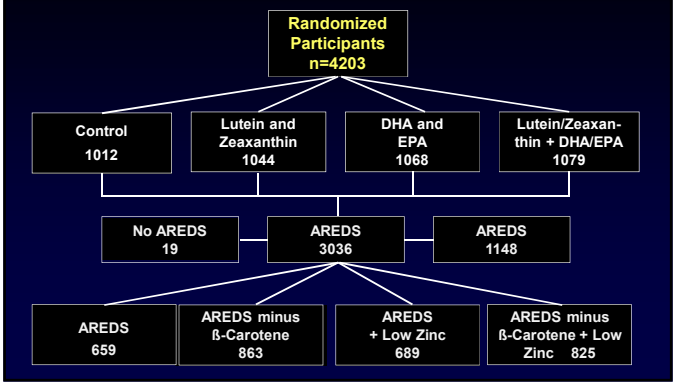
# AREDS 2

- Substudy evaluating the effectiveness of the omega-3 long-chain polyunsaturated fatty acids (fish oils):
  - Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)

# AREDS 2

- Pts will be randomized into 4 groups
  - Placebo;
  - Lutein and zeaxanthin only
  - Fatty acids only
  - Lutein and zeaxanthin plus fatty acids.
- During study visits and phone calls, patients will be asked about possible side effects.
- Pts will have an eye exam and photos at 1 yr
- 5 year follow up

## Study Design



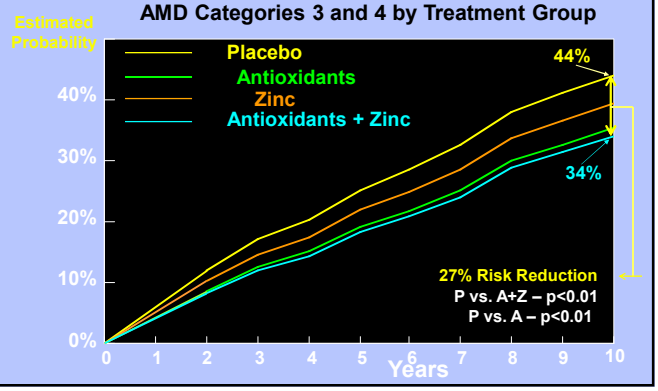

JAMA Ophthalmology — The JAMA Network

The Age-Related Eye Disease Study 2 Research Group

Lutein/Zeaxanthin for the Treatment of Age-Related Cataract: AREDS2 Randomized Trial Report No. 4

Published online May 5, 2013

## Long-Term Rates to Advanced AMD



Age-Related Eye Disease Study 2

## Conclusions

- Comparisons of the three active arms to control (primary analyses) did **not** significantly reduce risk of progression to AAMD
- The addition of lutein/zeaxanthin to the AREDS formulation as analyzed by the main effect showed 10% decrease in risk of progression to AAMD
- No main effect efficacy with DHA/EPA

Age-Related Eye Disease Study 2

## Conclusions

- Secondary randomization suggests no differences in the progression to AAMD for elimination of beta-carotene or lowering zinc dose
- No differences in adverse side-effects (gastrointestinal disorders or others) between "low" and high zinc groups
- Insufficient data to make recommendation for zinc

Age-Related Eye Disease Study 2

## Conclusions

- The main effect of lutein/zeaxanthin demonstrated 10% reduction of AAMD
- ~ 20% reduction in the risk of progression to AAMD of L/Z beyond the effects of AREDS supplement in persons with the lowest dietary intake of L/Z
- ~ 20% reduction in the risk of progression to AAMD, particularly neovascular AMD, of L/Z in head-to-head comparison with beta-carotene

Age-Related Eye Disease Study 2

## Conclusions

- Improve the safety of the AREDS supplements by removing beta-carotene to decrease the risk of lung cancer in smokers and former smokers who compose >50% of persons with AMD.

Age-Related Eye Disease Study 2

## Conclusions

- Considering the totality of evidence, lutein/zeaxanthin may be an appropriate carotenoid substitution for beta-carotene in the AREDS formulation

Age-Related Eye Disease Study 2

## 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)~~

## Central Retinal Vein Occlusion (CRVO)

- Common retinal vascular disorder with potentially blinding complications
  - Macular edema
  - Neovascularization leading to NVG
- Intraretinal hemorrhages in all 4 quadrants
- Dilated venous system
- Generalized disc edema
- 70 % Nonischemic vs 30% Ischemic

## Central Retinal Vein Occlusion Study (CVOS)

**Purpose:**

- To determine whether photocoagulation can help prevent iris neovascularization in eyes with CVO and evidence of ischemic retina
- To assess whether grid-pattern photocoagulation will reduce loss of VA due to macular edema
- To develop new data describing the course and prognosis for eyes with CVO

## CVOS

- 728 eyes from 725 patients
- Randomized to 4 study groups
  - Perfused
  - Nonperfused
  - Indeterminate perfusion
  - Macular edema

## CRVO Study: 3 Yr Natural History

- VA outcome dependent on initial acuity
  - Initial $\geq$20/40: 65 % maintained
  - VA < 20/200 initial : 80% chance VA $\leq$ at final
  - VA 20/50 to 20/200: 19% improved, 44% stayed in this range, 37% worse than 20/200

## CRVO Study: 3 Yr Natural History

- 34% initially perfused converted to ischemic
- INV/ANV developed in 16% of all eyes (117/714)
  - 56/117 were initially perfused
- 35% of nonperfused eyes developed INV/ANV

## Is Early (prophylactic) PRP Beneficial for Ischemic CVO?

- Prophylactic PRP dos not prevent INV or angle NV
- Both groups developed INV/ANV equally
- Prompt regression of INV/ANV is more likely to occur in eyes that have not been treated
- Close observation is recommended with frequent follow up in early months (q2 wks to q 1 mo)
  - Special attention to slit lamp exam of iris and gonioscopy

*Ophthalmology* October 1995, 102:1434-1444

## Is Grid Laser Tx Beneficial for Macular Edema in CVO ?

- 155 eyes, 77 received grid Tx, 78 observed
- VA ≤ 20/50
- Treatment reduced angiographic evidence of macular edema but...
- Visual acuity was not improved
- Results do not support a recommendation for laser Tx of macular edema in CVOS

*Ophthalmology* October 1995, 102:1425-1433

## CVOS: Summary

- There is no benefit in prophylactic PRP to prevent INV or ANV
- There was no benefit in laser Tx for Mac edema
- INV and ANV develops ~ 35% of nonperfused CVO; 16% of all CVO's
- Important natural history data for prognosis

## What about Intravitreal Kenalog for Macular Edema in Vein Occlusions?

## Conclusions

- Macular edema usually responds
  - Decreased edema can be detected with OCT as early as 2 days after injection
- Visual response depends on degree of macular ischemia/damage

## Conclusions

- Edema often re-accumulates 4-6 months after injection
- Injection can be safely repeated if edema returns
  - Secondary injections usually effective in decreasing edema again

## IVK vs. Standard Care

- Exciting new treatment with a lot of potential
- Hard to compare in the absence of randomized controlled clinical trials
- SCORE Study – NEI sponsored study
  - Standard Care vs Corticosteroid for Retinal Vein Occlusion (BRVO and CRVO)
  - Multicentered, Phase III clinical trial

## Optometric Management of CVO

- Good history identifying time of occurrence
- Rule out INV, ANV
- Establish risk factors for nonperfusion
  - VA< 20/200, APD, INV/ANV, CWS, Retinal Transp.
  - 4 months: 547 of 728 were perfused (75%)
- Perfused: follow every 1 months
- Nonperfused: initially q 2 weeks, then q month
- Refer to retinal specialist if unable to determine or development of any NV

*Thank You!*