Landmark Studies from the NEI: Impact on Disease Management

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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)

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

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

Clinical Trials from the NEI

DRS
ETDRS
MPS
CATT
BRVO Study
CRVO Study
SCORE
HEDS 1 and 2
OHTS
EMGT
CIGTS
AGIS
CITT
CLEK
COMS
ONTT

Clinical Trials from the NEI

DRS
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AREDS 1,2
OHTS
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CIGTS
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COMS
ONTT
HEDS I, II
EVS
SOCA
CLAMP
COMET
CLEERE
IONDT
LALES

Dr. Julius Stein speaks in favor of creating the NIH before the House subcommittees on Public Health and Welfare (November 1, 1967).
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

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 (Wisconsin Beaver Dam Eye Study)

Patients Affected

- 10% wet or exudative
- 90% dry or nonexudative
- VA < 20/200
- 80-90% exudative
- 10-20% dry

What We Now Know

- Genetic background
- Environmental/lifestyle risk factors
- The interaction between these variables, predispose to ARM.
Clinical Assessment + Genetics

**Complete set of Risk factors**

- Genetic Factors 60%
- Non-Gene Factors 40%

1. CFH
2. CF1
3. C2
4. CF2
5. C3
6. ARMS2
7. TIMP3*
8. COL8A1*
9. LIPC*
10. CETP*
11. ABCA1*
12. APOE

What is the role of nutritional supplements in AMD?

73 y/o Hispanic Female

3/2010

Smoker, h/o CVA, paralyzed on the R side

What is the role of Anti-oxidants on AMD?

- What are anti-oxidents?
  - Carotenoid pigments, Vit A, E, C and Selenium
- Are Carotenoid pigment 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
  - Provide protection via increased macular pigments

Function of the Carotenoids

- Protect against the oxidative damage
- Absorb/filter light
  - Absorbs damaging blue light
- Quench free radical formation

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

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: 3 Stages of AMD

- Early AMD
- Intermediate AMD
- Advanced

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-carotene and zinc”

Estimated Probability Rates to Advanced AMD

- AREDS 1 constituents:
  - 500 mg vitamin C
  - 400 IU vitamin E
  - 15 mg beta-carotene (25,000 IU)
  - 80 mg zinc
  - 2 mg copper

- 25% decrease risk reduction in developing advanced AMD (groups 3 and 4) with antioxidants plus zinc
Long-Term Rates to Advanced AMD

![Graph showing AMD categories 3 and 4 by treatment group over 10 years. Placebo has the highest risk, followed by Antioxidants, Zinc, and Antioxidants + Zinc. Estimated Probability is shown with Placebo at 44% and Antioxidants + Zinc at 34% after 10 years. 27% Risk Reduction is noted for Antioxidants + Zinc compared to Placebo.]

AREDS Results
Arch of Ophthalmol Oct 2001

- AREDS was unable to determine potential treatment benefits among early AMD pts
  - Slow progressive trend
  - Not likely to progress to an advance stage of AMD
  - These groups make up a large number of our pts

AREDS Results
Arch of Ophthalmol Oct 2001

- 592 Developed CNV, 257 developed geographic atrophy
- Group 1: Early AMD (1063 Pts)
  - Only 15 progressed over 5 yrs due to CNV or geographic atrophy: 1.3% probability
  - Projected 50
  - 316 progressed to group 2 and 3
- Group 2 and group 3: 834 total

More Questions than Answers…?

- What about Lutein and/or Zeaxanthin?
  - These were not available when the AREDS began – so they have not been studied…
- Macula contains large amounts of zeaxanthin
  - Might actually be a better carotenoid to study
  - This would avoid the problem of using beta carotene in smokers

AREDS2 Inclusion Criteria

- Bilateral Large Drusen or Late AMD in One Eye
  - Large Drusen
  - GA
  - NV AMD

Assess the effects of Lutein & Zeaxanthin on progression of AMD
- Inverse correlation between L/Z concentrations and risk of developing AMD
- ω-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid & eicosapentaenoic acid)
- Anti-inflammatory & anti-angiogenic properties

http://www.nei.nih.gov/ Eye Disease Study 2


http://www.nei.nih.gov
Age-Related Eye Disease Study 2 (AREDS2)

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 into 4 groups
  - Placebo
  - Lutein and zeaxanthin only
  - Fatty acids only
  - Lutein and zeaxanthin plus fatty acids.

Randomized Participants N=4,000

- Placebo N=1,000
- Lutein/zea N=1,000
- DHA/EPA N=1,000
- Lutein/zea DHA/EPA N=1,000

No AREDS Supplements
AREDS supplements

Lutein/zea DHA/EPA

Study Design

Randomized Participants n=4,203

Control 1012
Lutein and Zeaxanthin 1044
DHA and EPA 1068
Lutein/Zeaxanthin + DHA/EPA 1079
No AREDS 19
AREDS 3026
AREDS 1448
AREDS 659
AREDS minus Beta Carotene 683
AREDS = Low Zinc 689
AREDS minus Beta Carotene = Low Zinc 825

Estimated Probability of Progression to AAMD

- Placebo - AREDS 40%
- L/Z 32%
- DHA/EPA 30%
- L/Z & DHA/EPA 28%

AREDS 2: Primary Analysis

- Does adding lutein and zeaxanthin, DHA + EPA, or a combination of the two to the AREDS formulation reduced the risk of progression to advanced AMD?
  - Beyond the original 25%
  - Remember control group was taking original AREDS
AREDS 2

The Answer:
- The data did not demonstrate a significant reduction in progression to advanced AMD in any of the three treatment arms as compared to the control group.

So...
ARED 1 supplement just as good as AREDS 2

But...

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

Conclusions
- Secondary randomization suggests no differences in the progression to AMD 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 ---- Now wait a MINUTE!!

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.

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)
Genetic Testing in AMD

Macula Risk (Atic Dx)
Retnagene
Purchased by Nicox:
Relaunched in June 2014

Clinical Assessment + Genetics

Complete set of Risk factors

1. CFH
2. CFI
3. C2
4. CFB
5. C3
6. ARMS2
7. TIMP3*
8. COL8A1
9. LIPC*
10. CETP*

Key Genes Involved in the Development of AMD

What is the Relationship between Genetics, AMD and AREDS Supplement?

CFH and ARMS2 Genetic Polymorphisms Predict Response to Antioxidants and Zinc in Patients with Age-related Macular Degeneration

Patients with genetically determined CFH high risk alleles, zinc was associated with increased progression to advanced AMD

Patients with ARMS2 high risk alleles, zinc was associated with DECREASED progression to advanced AMD antioxidants worsened the outcome

Patients with CFH risk alleles benefit from antioxidants without zinc but patients with ARMS2 risk alleles benefit from zinc without antioxidant
49% derive more benefit from treatment other than AREDS

Genetic Testing and Recommending Nutritional Supplements
- Of the estimated 15 million Americans taking the AREDS formula, more than ten million should not be on either zinc or antioxidants
- Only about 23% of patients taking AREDS formula should be while the vast majority should not
- Genotype-directed therapy of the study population would have more than doubled the reduction in AMD progression rate compared to treatment with the AREDS formulation

Treatment for Wet AMD

Intravitreal Formulation: Lucentis
ANCHOR at 24 Months:
Mean Change in Visual Acuity Over Time

Avastin® (bevacizumab, Genentech Inc.)
First anti-VEGF therapy approved by the FDA

Preparation of Intravitreal Bevacizumab at the Bascom Palmer Eye Institute

Lucentis vs. Avastin (Genentech vs Genentech)

COST
- Lucentis -> $2,500 - $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

Avastin vs. Lucentis
What is the 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

Highlights
- 1208 Pts Randomized
- Equivalent VA outcomes: Ranibizumab vs. Bevacizumab
  - Lucentis gained 8.5 letters vs. Avastin 8 letters
- Equivalent VA outcomes: monthly vs. PRN ranibizumab
- Inconclusive/ significant difference in VA Bevacizumab monthly vs PRN

4/28/2011, NEJM.org
Statistics From CATT 1 Year Results

<table>
<thead>
<tr>
<th></th>
<th>Lucentis Monthly</th>
<th>Lucentis PRN</th>
<th>Avastin Monthly</th>
<th>Avastin PRN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average change in acuity (letters gained)</td>
<td>8.5</td>
<td>6.8</td>
<td>8.0</td>
<td>5.9</td>
</tr>
<tr>
<td>Average ending visual acuity score (mean no. of letters)</td>
<td>68.8</td>
<td>68.4</td>
<td>68.4</td>
<td>66.5</td>
</tr>
<tr>
<td>Decrease in CMT (µm)</td>
<td>196</td>
<td>168</td>
<td>164</td>
<td>152</td>
</tr>
<tr>
<td>Number treatments needed</td>
<td>11.7</td>
<td>6.9</td>
<td>11.9</td>
<td>7.7</td>
</tr>
<tr>
<td>Systemic adverse events (TIA, MI, CVA, HTN)</td>
<td>6.9%</td>
<td>7.1%</td>
<td>8.0%</td>
<td>10.4%</td>
</tr>
</tbody>
</table>

CMT=central macular thickness  
CV A=cardiovascular accident  
HTN=hypertensive nephropathy  
MI=myocardial infarction  
TIA=transient ischemic attack


CATT: 2 Year Results

- 1,107 patients followed for yr 2
- Pts initially assigned to monthly treatment were reassigned randomly to monthly or as-needed
- Mean gain in VA was similar for both
- Mean gain > for monthly treatment than for as-needed (difference, -2.4 letters; 95% CI)
- The proportion of patients without fluid:
  - 13.9% in the bevacizumab as-needed group
  - 45.5% in the ranibizumab monthly

ARVO May 2012

CATT: 2 Year Results

Other interesting tidbits:
- Estimated 2-year drug cost per patient:
  - $705 in the bevacizumab as-needed group to $44,800 in the ranibizumab monthly group.
- Proportion of eyes with geographic atrophy at 2 years ranged:
  - 25.8% in the ranibizumab monthly group
  - 12.9% in the bevacizumab as-needed group

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 greater 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
**3376 Patients Observed in NEI and GRF Clinical Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Dx</th>
<th>Randomization</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMGT1</td>
<td>255 pts</td>
<td>OAG</td>
<td>Tx (ALT + betaxolol) vs observation</td>
<td>4-9 years</td>
</tr>
<tr>
<td>OHTS2</td>
<td>1636 pts</td>
<td>OHT</td>
<td>Medical Tx vs observation</td>
<td>5 years</td>
</tr>
<tr>
<td>CIGTS3</td>
<td>607 pts</td>
<td>OAG</td>
<td>Medical Tx vs surgery</td>
<td>5 years</td>
</tr>
<tr>
<td>AGIS4</td>
<td>738 eyes</td>
<td>OAG</td>
<td>ALT vs surgery</td>
<td>8 years</td>
</tr>
<tr>
<td>CNTGS5</td>
<td>140 eyes</td>
<td>NTG</td>
<td>Medical Tx and/or surgery vs observation</td>
<td>7 years</td>
</tr>
</tbody>
</table>

ALT = argon laser trabeculoplasty; NTG = normal-tension glaucoma.


**Tania: 44 y/o Hispanic Female**

- Has been seen several times over the yrs for routine eye care
- 1998: TA 20/22
- 09/05: TA 18/20
- 12/07: 19/20

**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

**Tania: 44 y/o Hispanic Female**

- 12/08: TA: 25/21
  - Pach: 610/620 µ
  - OCT done 1/5/08 – for review
- 4/20/09: TA 23/24
- 4/19/10: TA 23/25
- 10/11/2010: TA 22/23

**Ocular Hypertension Treatment Study (OHTS)**

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

**2009**

**Tania**

- Ocular HTN
  - No treatment
  - Is there a reason to justify treating her?
- What is her risk for developing glaucoma?
  - 5 yrs vs. lifetime?
**OHTS**  
*Arch Ophthalmol*  
June 2002;120:701-713

- 1636 participants randomized, followed 60 mo  
  - Observation vs Treatment  
- Goal: Reduce IOP 20% or IOP ≤ 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 Ophthalmology*  
June 2002;120:701-713

- Treatment reduced the chance of developing glaucoma by ≥ 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

**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 Central Corneal Thickness and Baseline Vertical C/D Ratio in Observation Group

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

Tania: 47 y/o: Oct 25, 2011
◆ TA: 24/23

10/25/11

4/09
Tania: 47 y/o:

4/20/2009

What would you estimate c/d to be?

Oct 25, 2011

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

Detection and Prognostic Significance of Optic Disc Hemorrhages during the Ocular Hypertension Treatment Study

Main Outcome Measures: incidence of optic disc hemorrhages and POAG endpoints.

Results: Median follow-up was 98.5 months. Stereoophotography-confirmed glaucomatous optic disc hemorrhages were detected in 128 eyes of 101 participants before the POAG and point. Twenty-one cases (17%) of POAG occurred in the treated group and 22 cases (18%) occurred in the untreated group. The cumulative incidence of POAG in the treated group was 8.4%, in the untreated group 16.1%. A review of all 128 hemorrhages revealed that 107 (84%) were detected only by review of photographs (P < 0.001). Baseline factors associated with disc hemorrhages were older age, thinner nerves, larger cup-to-disc ratio, larger pattern standard deviation index on perimetry, family history of glaucoma, and smoking status. The occurrence of a disc hemorrhage increased the risk of developing POAG.

Detection and Prognostic Significance of Optic Disc Hemorrhages during the Ocular Hypertension Treatment Study

Disc hemorrhages detected in 128 eyes of 123 participants

21 cases detected by both doctor and photos

107 cases (84%) were detected only by a review of photography
Of Note:

Incidence of Progressing to POAG
- No Disc Heme: 5.2%
- + Disc Heme: 13.6%
- Presence of a disc heme increase risk of developing POAG 6 fold

IOP and Glaucoma
- Lowering IOP < rate of glaucomatous ON damage….or does it?
  - Does it even matter….?
  - How low does IOP need to be?

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 Hispanic Female
Initial Presentation
- Her IOP is too high
- She needs to be treated
- If we don’t treat her, she has a considerable risk of going blind
Luisa: IOP: 26/27 mmHg

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

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. Medical Tx 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


EMGT

- 1st randomized, controlled, clinical trial to evaluate the effect of lowering IOP on progression of newly detected OAG
- Compared rate of progression in initially Tx eyes vs. untreated patients
- Try to quantify the effect of immediate IOP-lowering on progression
- Identify factors related to progression

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

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

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

**EMGT Results**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP at 3 month follow-up</td>
<td>15.5</td>
<td>20.8</td>
</tr>
<tr>
<td>Percentile change in IOP</td>
<td>25%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

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

**EMGT Progression**

<table>
<thead>
<tr>
<th>Progression</th>
<th>Treated</th>
<th>Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Yr Progression</td>
<td>44%</td>
<td>66%</td>
</tr>
<tr>
<td>8 Yr Progression</td>
<td>59%</td>
<td>76%</td>
</tr>
</tbody>
</table>

Baseline factors that predicted progression on a multivariate analysis:
- Higher IOP
- Exfoliation
- Worse MD
- Older age
- Frequent disc hemorrhages


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

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 y/o patient diagnosed with glaucoma is expected to live 12 years
- He/she will lose ~ 4.2 dB during his remaining lifetime
- This patient will likely not "get in trouble" unless he starts with MD of \leq 10 dB

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 anti-fibrolytic agents on 2nd surgery

Advanced Glaucoma Intervention Study (AGIS)

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

Juan 4 yo Hispanic Male

- Parents are concerned that the RE might be a “lazy eye.”
  - That eye just doesn’t seem to see as well
- VA: 20/70 RE; 20/20 LE
- Cover test: Orthophoria, full EOM’s
- Cycloplegic Retinoscopy
  - R: +400 DS
  - L: +1.00 DS

Juan 4 yo Hispanic Male

Impression
- Anisometria with Amblyopia RE

Plan
- Give Rx
- RTC 4 weeks
- Consider patching

Juan 4 yo Hispanic Male

4 Weeks Later
- Wearing the glasses
- VA: 20/40 RE; 20/20 LE
- What now?
- Patch...but he won’t wear the patch
- Patching fails
Amblyopia

- What is the role of Atropine drops in the treatment of amblyopia?
- How long does a child need to wear a patch for it to be effective?
- At what age is therapy still effective?

Amblyopia Treatment Study I (ATS I)

- To determine if the success with atropine is equivalent to occlusion (patching) therapy
- To develop more precise estimates of the success rates of amblyopia treatment
- To identify factors that may be associated with successful treatment of amblyopia
- To collect data on the course of treated amblyopia

ATS I

- Children with amblyopia < 7 years old
  - Due to strabismus or anisometropia
- VA in amblyopic eye 20/40 - 20/100
  - VA in fellow eye 20/40 or better
- There must be > 3 lines of acuity difference
- Patients must have had < 2 months of amblyopia therapy in the past 2 years.

ATS I: 6 Months Results

- 419 pts, average age of 5.3 yrs
- 215 in the patching group and 204 in atropine group
- Mean VA in the amblyopic eye at enrollment was approximately 20/63
- Mean difference in VA b/w eyes: 4.4 lines


ATS I: 6 month Results

- VA improved by about 3 lines in both groups
- Improvement was initially faster in the patching group
  - After 6 mo, the difference in VA b/w groups was small
- The mean VA (Snellen approximation) was 20/32 in the patching group and 20/32-2 the A1 group
  - This small difference was not statistically significant

ATS I:

- How long do you need to patch for it to be affective?
ATS

- 189 children < 7 yrs old
  - Average age was 5.2 yrs
- Moderate amblyopia
- Randomized: 2 hrs vs 6 hrs of patching
  - 95 2 hr vs 94 6 hr
- Both groups showed significant improvement in the vision (amblyopia)
- 4 mo: 79% in 2 hr group vs 76% in the 6 hr group had a 2.4 lines improvement

ATS I

- Patching children with moderate amblyopia for 2 hours daily works as well as patching for 6 hours

May 2003 issue of *Arch of Ophthalmology*

ATS

- Doing near work while wearing the patch was critical
  - For at least 1 hr
- May not apply to children with very dense amblyopia

ATS I: 24 Mo Follow up Results

*Arch Ophthalmol.* 2005 Feb;123(2):149-57

- Treatment affect of Patching vs Atropine for 6 months was sustained
- 2 years – VA in the amblyopic eye improved from baseline 3.7 lines (patching) 3.6 lines (atropine group)
- VA was ~ 20/32 in amblyopic eye in both groups - 1.8 lines worse than the 20/20 eye

ATS II: Severe Amblyopia

*Ophthalmology,* Nov 2003

- Patching for Severe Amblyopia
  - Defined as reduction in VA 20/100 to 20/400
- 175 kids 3 to < 7 yo randomized @ 32 centers
  - Full time patching vs 6 hrs patching
    - Both groups required 1 hr of near work
- 4 months: VA improved the same in both groups
  - 4.8 lines in the 6-hour group
  - 4.7 lines in the full-time group (P = 0.45)
- 6 hrs of daily patching = to the improvement produced by full-time patching

Juan 12 yo Hispanic Male

- Failed a school screening
- VA: 20/70 RE; 20/20 LE
- Cover test: Orthophoria, full EOM’s
- Cycloplegic Retinoscopy
  - R: + 400 DS
  - L: + 1.00 DS
Randomized Trial of Treatment of Amblyopia in Children aged 7 to 17 years
- 507 pts from 49 clinical sites randomized
- VA 20/40 to 20/400 optimized optical Rx
- Treatment group:
  - 2-6 hours per day of patching combined with near visual activities for all patients
  - Atropine for children 7 to 12 years
- Control group: optical correction alone

Treatment of Amblyopia in Children Aged 7 to 17 years
Success defined as:
VA improved > 10 or more letters (2 lines)
by 24 wks were considered responders

- 7-12 yr olds: n = 404
  - 53% of the treatment group vs. 25% of the optical correction group were responders (P<.001)
- 13-17 yr olds: n = 103
  - 25% and 23% were responders (adjusted P = .22)
  - Patients not previously treated: 47% vs. 20%,
    (adjusted P = .03)
- Most patients, including responders, were left with a residual visual acuity deficit.

Treatment of Amblyopia in Children Aged 7 to 17 years

- 7-12 yr olds
  - There is a benefit for amblyopia therapy while performing near visual activities even if the amblyopia has been previously treated
- 13-17 yr olds
  - Is a benefit for eyes not previously treated for amblyopia
  - If previously amblyopia -> No benefit
- It is not known if therapy will be sustained

NEI Summary
- NEI has been THE leader in delivering the most up-to-date scientific information for treating and managing eye disease
- The studies are relevant to what clinicians see every day in their practices