TOP TEN AMD STORIES OF 2008

(and early 2009)

10. TOPICAL THERAPY

A. Will not discuss in detail here. See prior lecture for more info

B. Topical therapy is coming. A number of drugs for both wet and dry AMD are in the pipeline

C. Will revolutionize care of AMD

- Prophylactic therapy
- Role of Optometry
- Contingency therapy

9. BASELINE CHARACTERISTICS

A. AREDS: Progression Risk Factors

- Presented in a paper by Dr Emily Chew at 2008 AAO Meeting
- http://www.osnsupersite.com/view.aspx?rid=36107
- Significant predictors of disease progression:
  - severity of AMD at initial presentation,
  - smoking,
  - age and
  - AREDS-formula supplement treatment
- No large drusen in either eye at the initial exam: rate of advanced AMD at 10 years = 1.1%
- Large drusen or pigmentary changes in one eye or both eyes at initial exam: the rate of advanced AMD at 10 years = 72%
- Persons predisposed to progression have more severe AMD right from the start.
  - genetic predisposition to advanced AMD.
  - it may be possible for clinicians to identify at-risk patients early, and offer them more intensive care to slow progression and/or detect the onset of treatable lesions earlier.

B. Patients with initial better vision need fewer injections

- presented in a paper by Dr Jay S. Duker at the Retina 2009 meeting in January

- those patients with AMD who show full resolution of macular fluid with a single injection of Lucentis (ranibizumab) have better baseline characteristics than those patients who require multiple injections to achieve full resolution.
- a retrospective study of 62 patients who were followed over 1 year after receiving an injection of Lucentis. Patients were re-treated as deemed necessary by the surgeon.
- Sixteen patients (31%) needed only one injection to achieve full resolution of fluid. These 16 patients had an initial visual acuity of 20/66 and an optical coherence tomography measurement of 263 um
  - two-injection group at 20/76 and 279 um,
  - the three-injection group at 20/80 and 297 um
  - the four-injection group at 20/93 and 410 um.
- These results suggest that patients who present sooner for care, when the choroidal neovascular lesion is smaller, and vision is better, tend to need fewer anti-VEGF injections.
- This is another reason to encourage patients with AMD to closely monitor their vision to detect the earliest symptoms of choroidal neovascularization.

C. CAPT Study: Earlier detection with closer monitoring

- Maguire M, et al. Characteristics of choroidal neovascularization in the complications of age-related macular degeneration prevention trial. Ophthalmology 2008;115:1468–1473
- http://www.ncbi.nlm.nih.gov/sites/entrez/18486222
- close monitoring of patients with AMD can improve the ability to detect choroidal neovascularization (CNV) while it is still outside the fovea and vision is still good
- Results of 5 or more years of follow-up data from 1052 participants in the Complications of Age-related Macular Degeneration Prevention Trial (CAPT) were analyzed. These individuals had bilateral drusen and visual acuity of 20/40 or better at beginning of the study period.
- At the time of detection, 153 (54%) were subfoveal, and 157 (56%) were less than or equal to 2 disc areas in size. Visual acuity was 20/40 or better in 123 (69%) of 179 eyes with visual acuity measured at the time of detection.

- The authors write "close monitoring of high-risk eyes, such as fellow eyes in patients with unilateral CNV or eyes with multiple large drusen and pigmentary changes, can lead to detection of CNV when it is more likely to be outside the fovea, relatively small, and without a large loss in visual acuity. Regular retinal examinations, optical coherence tomography, preferential hyperacuity perimetry, and use of the Amsler grid may aid in early detection of CNV."
- It is extremely important that patients at risk for CNV check their vision regularly for symptoms of CNV. With currently available treatments (such as Lucentis), it is very likely that vision can be improved (or at least maintained) after CNV is found and treated. Nowadays, much of the vision lost to CNV is lost prior to the initiation of treatment. If CNV is found early, while vision is still good, the good vision can usually be maintained.

8. MODIFIABLE RISK FACTORS

A. Beaver Dam Eye Study: Smoking

- Klein, et al. Further Observations on the Association Between Smoking and the Long-term Incidence and Progression of Age-related Macular Degeneration Arch Ophthalmol. 2008;126(1):115-121.
- http://www.ncbi.nlm.nih.gov/pubmed/18195228
- Smokers had a 47 percent increase in their odds of developing early AMD
- They also developed AMD at a younger age (69.2 years) than former smokers (72.3 years) and those who had never smoked (74.4 years).
- Smoking at the beginning of the study was also associated with the cumulative progression of AMD over the 15 years of the study.
- Exposure to environmental (second-hand) smoke was also not associated with AMD
    - EU political movement underway to place warnings on cigarette packets about the risk of blindness.
    - "We are seeking to convince the European Commission of the public health importance of the hazards of smoking on the eyes and for warnings along those lines to now appear on cigarette packets."

B. Atherosclerosis Risk in Communities Study: Obesity

- Peeters A, et al. Changes in abdominal obesity and age-related macular degeneration: the Atherosclerosis Risk in Communities Study. Arch Ophthalmol. 2008 Nov;126(11):1554-60
- http://www.ncbi.nlm.nih.gov/pubmed/19001224
- Decreasing abdominal obesity results in a lower risk for age-related macular degeneration (AMD), according to a new study.
- The waist-hip ratio (WHR) is a measure of central (abdominal) obesity.
  - The WHR is calculated by dividing the waist circumference (maximum girth at the belly button) by the hip circumference (maximum girth at the buttocks).
  - A WHR of 0.7 for women and 0.9 for men have been shown to correlate strongly with good general health.
- It was found that the group with the greatest decrease in WHR had a 29% lower risk of having AMD.
- Among participants who were obese at baseline, persons with the greatest decrease in WHR had a 59% lower risk of AMD.
- The investigators conclude that middle-aged persons with a 3% or greater reduction in WHR over time were less likely to have AMD, particularly among those who were initially obese.
- "Our findings suggest a role of weight loss in preventing the development of AMD."

C. Vigorous Physical Activity Decreases Risk of AMD

- Williams PT. Prospective study of incident age-related macular degeneration in relation to vigorous physical activity during a 7-year follow-up. Invest Ophthalmol Vis Sci. 2009;50:101-6.
- http://www.ncbi.nlm.nih.gov/pubmed/18566466
- A new study finds that running has a significant protective effect on the development of AMD.
- Over 40,000 runners were followed prospectively for 7.7 years. The participants self-reported their running habits and whether or not they had been clinically diagnosed with AMD.
- The participants who developed AMD ran significantly less than those who remained unaffected.

- When adjusted for age, sex, diet, and smoking history, the relative risk for AMD decreased 10% per for every kilometer per day (km/d) that the person ran.
- Compared with the participants who averaged <2 km/d:
  - Running 2-4 km/d had 19% lower risk,
  - Running 4 km/d had 42% to 54% lower risk.
- The authors conclude that vigorous exercise is associated with a lower incidence of AMD independent of weight, cardiorespiratory fitness, and cigarette use.
- Regular aerobic exercise will reduce the risk of high blood pressure, heart disease, and stroke. There is good evidence linking cardiovascular disease with AMD. The two diseases share common risk factors, such as obesity and smoking. Given how beneficial vigorous exercise is for cardiovascular health, it may not be too surprising to learn that it may also cut the risk of AMD

D. Links between AMD and CVD

- Recently, several studies have helped to cement the bond between age-related macular degeneration (AMD) and cardiovascular disease (CVD).
- Researchers have added to the list of possible common risk factors: blood pressure, body mass index and cholesterol.
- Exactly how the two diseases are related is still an unanswered question. Possibilities include:
  - inflammatory processes
  - antioxidants
  - omega-3 fatty acids
- improved and early management of cardiovascular disease could reduce the risk of developing late stages of AMD
  - what’s good for the heart is good for the eye

7. CATARACT AND AMD

A. Sunlight and AMD

- Fletcher AE, et al. Sunlight exposure, antioxidants, and age-related macular degeneration. Arch Ophthalmol. 2008;126:1396-403.
- http://www.ncbi.nlm.nih.gov/pubmed/18852418

- A population-based study finds that sunlight exposure increases the risk of wet AMD in those people with low serum antioxidant levels.
- Concerns have been raised regarding the potential of cataract surgery to accelerate progression to advanced, vision-threatening forms of AMD. Largely because of the findings from two large epidemiologic studies of an adverse association of cataract surgery with AMD, some investigators have speculated on the risk of cataract surgery in eyes at risk for development of advanced AMD.
- This is the first study to find an adverse association of blue light exposure with neovascular AMD in humans with low serum levels of antioxidants.
- This study consisted of 4753 persons aged 65 years or older. Adult lifetime sunlight exposure was estimated by combining meteorologic and questionnaire data. Blood samples were analyzed for antioxidant levels.
- No association was observed unless both antioxidant levels and sunlight exposure was taken into account.
  - Consistent pattern of increased risk of neovascular AMD with increased blue light exposure among participants with the lowest serum levels of antioxidants.
- Low levels of certain combinations of antioxidants, especially vitamin C, vitamin E, and zeaxanthin, showed highest risk
- The combination of blue light exposure in the presence of low levels of zeaxanthin, vitamin E, and vitamin C was associated with a nearly 4-fold increased risk of neovascular AMD.
- Because high levels of antioxidants were generally not protective, no special antioxidant supplement was recommended.
  - The researchers recommend that people follow standard dietary guidelines to ensure adequate antioxidant levels.
- It appears that our eyes may be able to tolerate sunlight exposure if there are adequate levels of antioxidants to protect them

B. Blue-blocker IOLs impair vision

- A new study reports that color perception and contrast sensitivity may be impaired by blue-light-filtering intraocular lens implants.

- This study included 48 eyes of 24 consecutive patients with age-related cataract. Each patient had standard cataract surgery with IOL implantation. Patients received a blue-light-filtering IOL in one eye and a UV-filtering IOL in their other eye.
- The investigators found that blue-light-filtering IOLs had worse contrast acuity and lower foveal thresholds compared with the UV-filtering IOLs. On questioning, only 3 of 24 patients noticed a difference in the quality of their vision between their eyes.
- The researchers conclude that blue-light-filtering IOLs negatively affect contrast acuity and blue/yellow foveal threshold when compared with UV-filtering IOLs.
- Intended as a way to decrease the risk of AMD following cataract surgery, the negative consequences of blue-blocking IOLs may out weight any theoretical advantage.
    - First, it is important to recognize that there is no clinical or experimental proof that normal sunlight exposure causes AMD.
    - The Centers for Medicare and Medicaid Services concluded that "the relationship between blue light and AMD is speculative and not proven by available evidence."
    - Furthermore, It has been suggested that yellow-tinted implants may upset the circadian rhythm. Sunlight is important in setting the body’s internal clock, known as the circadian rhythm.
    - Insufficient sunlight exposure may result in insomnia, daytime sleepiness, depression, and poor concentration.
    - The ideal IOL for circadian health should transmit as much blue light as possible. Blue-blocking IOLs provide 27% to 38% less circadian sensitivity than UV-blocking IOLs.
- The current study indicates that blue-blocking IOLs may impair visual function in some patients.
- Unless stronger evidence emerges linking sunlight exposure to AMD, blue-blocking IOLs may not be such a great idea.

C. AREDS: CE does not increase the risk of AMD progression

- Chew EY, et al. Risk of advanced age-related macular degeneration after cataract surgery in the Age-Related

Eye Disease Study: AREDS report 25. Ophthalmology. 2009 Feb;116(2):297-303

- http://www.ncbi.nlm.nih.gov/pubmed/19091420
- The AREDS study finds that there is no clinically important increased risk of progression to advanced AMD after cataract surgery.
- The investigators analyzed the relationship between cataract surgery and the development of advanced AMD (neovascular or geographic atrophy) in 4577 participants (8050 eyes) from the AREDS clinical trial.
- Results from statistical analysis were not significant and there are no consistent trends among models.
- The absence of any consistent pattern in the direction of harm across models reinforces the conclusion that AREDS data provide little evidence that cataract surgery increases the risk of progression to late AMD.
- These results are contrary to the results of some previously published epidemiologic studies, including 2 reports that each pooled data from different population-based studies.
- There are many differences between the AREDS study and earlier studies that found an association between cataract surgery and progression of AMD.
    - AREDS participants were selected on the basis of having a high risk of developing advanced AMD. More than 40% of the AREDS cohort had high-risk characteristics for late AMD. The inclusion of such a high proportion of participants who had a propensity for advanced AMD to develop might have decreased the ability to detect additional risk factors, such as the impact of cataract surgery.
    - AREDS participants, with their more recent surgery, were probably more likely to have had ultraviolet B-blocking lens implants inserted than persons who had lenses implanted earlier. Insertion of such lenses may decrease the risk of AMD. Thus, the greater likelihood of extracapsular cataract extractions with insertion of ultraviolet-blocking lenses in AREDS participants may explain some of the differences in findings.
- The AREDS data suggest that there is no clinically important increased risk of progression to advanced AMD after cataract surgery.

    - This is the only prospective study in which the severity of AMD was documented before and after cataract surgery in a large number of cases with more than 5 years of regular follow-up.
    - These data, which are contrary to that of previously reported results, may provide some reassurance to patients with AMD who are considering cataract surgery.

6. PHOTODYNAMIC THERAPY

A. PDT plus intravitreal steroids: Two year results

- Piermarocchi S, et al. Combination of photodynamic therapy and intraocular triamcinolone for exudative age-related macular degeneration and long-term chorioretinal macular atrophy. Arch Ophthalmol. 2008 Oct;126(10):1367-74.
- http://www.ncbi.nlm.nih.gov/pubmed/18852414
- Photodynamic therapy (PDT), when combined with intravitreal steroid injection will initially improve vision in patients with wet AMD, but these improvements are lost over a 24-month follow-up period.
- Eighty-four patients were enrolled to receive PDT (n = 41) or PDT plus steroid therapy (n = 43). Patients were then followed for 24 months.
- Visual acuity improved at the 1 month follow-up visit in both groups, but then progressively decreased in both groups.
    - The visual acuity worsened more rapidly in the PDT-only group.
    - At the 24-month visit the PDT plus steroid group showed significant worsening of vision, reaching values statistically similar to the PDT-only group.
- The researchers conclude that after an initial visual acuity benefit that lasts for at least 1 year, combination therapy is associated with progressive visual decline during the second year of follow-up.
- After 2 years, there was no significant difference in the vision between the two treatment groups
    - both groups had significantly worse vision than at the time of the initial treatment.

- This study casts doubt over the long-term vision benefits of photodynamic therapy.
  - Although numerous studies have demonstrated the potential benefits of steroid-PDT combination therapy, this long-term study clearly demonstrates that these benefits may be transient.
  - The authors remind us that at least 2 years of follow-up is necessary evaluate the lasting effects of any new treatment for wet AMD.

5. RETINAL PROSTHESES

A. Concepts

- Generate phosphenes through direct electrical stimulation of retinal cells.
- The prospects for retinal prostheses to provide some visual substitution to those blinded by RP or AMD in general appear promising.
  - none of the prosthesis systems currently being developed will restore anything resembling normal vision
- Epiretinal implant: Stimulate ganglion cells
- Subretinal implant: Stimulate cells of the inner nuclear layer (bipolar, amacrine, horizontal, etc)

B. Engineering Approaches

- Implanted Multielectrode Array (MEA)
  - Implant stimulating electrodes
  - use transcutaneous telemetry to transfer data and power to them.
  - Image capture and processing takes place externally.
  - Usually implanted epiretinally and stimulate retinal ganglion cells directly.
- Microphotodiode array (MPDA)
  - Implant optoelectronic devices that directly convert light into electricity.
  - Usually implanted subretinally, as artificial photoreceptors.
  - Takes advantage of existing image processing functions of the retina.
- Biochemical prosthesis

    - virally re-engineering ganglion and/or bipolar cells to become light sensitive.
    - Early development, at least 5 years away from commercialization.

C. Commercial Development

- Over 20 research groups and companies actively developieng retinal prosthetics
- Ongoing long-term implantation clinical trials
    - Second Sight
        - Epiretinal MEA
        - Argus I: 16-electrode device
        - Argus II: 60-electrode device (improved spatial recolution)
    - Intelligent Medical Implants
        - Epiretinal MEA
        - Features an “adaptive retinal encoder” to assist with adjustment of stimulation parameters for individual patients
    - Epiret
        - Epiretinal 25-electrode MEA
- Three companies aim to release commercial devices before the end of 2010:
    - Second Sight
    - Intelligent Medical Implants
    - Retina Implant
        - Subretinal MPDA
        - Hybrid device incorporating both light amplification and electrical stimulation functions

4. LUTEIN

A. LUNA: Supplementation increases macular pigment

- Zeimer M, et al. [The macular pigment: short- and intermediate-term changes of macular pigment optical density following supplementation with lutein and zeaxanthin and co-antioxidants : The LUNA Study.] Ophthalmologe. 2009;106:29-36.
- http://www.ncbi.nlm.nih.gov/pubmed/18551295
- Researchers find only a slight decline in macular pigment levels 9 months after subjects stopped taking supplements containing lutein and zeaxanthin.

- The study included 108 subjects with and without AMD age 51-87 years that received a supplement containing 12 mg lutein and 1 mg zeaxanthin once per day (Ocuvite lutein) for 6 months.
  - Analysis of macular pigment optical density (MPOD) was performed during the period of supplementation and again 3, 6, and 9 months following discontinuation of the supplement.
  - A control group of 28 subjects received no dietary supplement.
- At baseline, the mean MPOD at 0.5 degrees was 0.50 in the supplemented group.
  - Following supplementation MPOD levels rose
  - 3 months after discontinuation of supplementation the highest levels of MPOD (0.59 ODU) were detected, a statistically significant increase.
  - Six months after supplement discontinuation, a slight decrease of mean MPOD occurred (to 0.54 ODU)
  - followed again by a slight increase 3 months later (to 0.57 ODU).
- The researchers conclude that supplementation of lutein and zeaxanthin leads to an increase of MPOD.
  - This effect outlasts the duration of intake, and 9 months after supplementation was stopped, the mean MPOD was still elevated compared with baseline levels.
- High doses of lutein and zeaxanthin seem to be necessary to increase macular pigment density in the retina; afterwards, the amount of carotenoids needed to maintain high concentrations seems to be covered by daily food.
- This study suggests that long-term lutein supplementation may be unnecessary to reap the benefits of increased macular pigment optical density.
  - Evidently, once the supplement has done it’s job and increased the amount of pigment in the macula, then the low levels of lutein that are present in a healthy diet may be sufficient to maintain these gains.
  - While more research is needed before recommending that patients stop taking lutein supplements after 6 months, this is good news for those patients that “drop out” of supplementation programs.

B. Lutein not protective against early AMD

- Cho E, et al. Prospective study of lutein/zeaxanthin intake and risk of age-related macular degeneration. Am J Clin Nutr. 2008;87:1837-43
- http://www.ncbi.nlm.nih.gov/pubmed/18541575
- A prospective study of dietary habits and health status failed to find an association between lutein/zeaxanthin intake and early AMD.
- The study analyzed data from the consisted of the Nurses' Health Study (NHS) and The Health Professionals Follow-up Study.
    - Involved prospective follow-up of 71,494 women and 41,564 men aged 50 years and older. Diet was assessed with a food-frequency questionnaire.
- During up to 18 years of follow-up, there were 673 cases of early AMD and 442 incident cases of neovascular AMD.
- Lutein/zeaxanthin intake was not associated with the risk of self-reported early AMD.
- There was a statistically nonsignificant and nonlinear association between higher lutein/zeaxanthin intake and lower risk of neovascular AMD.
- The authors conclude that these data do not support a protective role of lutein/zeaxanthin intake on risk of early AMD.
- The possibility of a protective effect for neovascular AMD needs to be examined further.
- We still lack good research that demonstrates whether lutein intake has a significant impact on the onset and progression of AMD.
    - We know that lutein supplementation will increase macular pigment, but whether that translates into lower incidence of AMD is still unclear.
    - Nonetheless, we continue to recommend lutein to our patients

3. ANTI-VEGF THERAPY

A. Evolving anti-VEGF treatment protocols

- Despite the excellent outcomes of injecting ranibizumab (Lucentis) monthly as seen in the MARINA and ANCHOR trials, such a schedule is not generally

desirable, because it is time-consuming, costly, and increases the risk of side effects from injection.

- The question of the necessity of monthly injections has been investigated in the PIER and PrONTO studies.
- PIER Study
  - Sought to address the dosing frequency issue by treating patients with 3 monthly doses followed by quarterly injections for the next 21 months.
  - Treated patients experienced better outcomes than control patients, but the results were not as impressive as those seen from the monthly dosing of the MARINA and ANCHOR trials.
- PrONTO Study
  - Was designed to reduce treatment frequency by establishing 5 criteria that include fluorescein angiography and OCT for re-treatment with Lucentis.
  - Outcomes in the PrONTO study were similar to those in the MARINA and ANCHOR trials, with about 35% of patients gaining at least 15 letters.
  - However, the amount of testing performed in PrONTO may not be practical in a busy clinic, and modified criteria are often used by practicing clinicians.
- Treat and Extend Protocol
  - Developed to rely on biomicroscopy and OCT findings to determine the need for re-treatment.
  - For every visit in which patients do not show exudative changes, their follow-up injection is extended by an additional 2 weeks.
  - If changes are seen, patients are asked to shorten the next visit interval by 2 weeks. However, treatments are never more frequent than 4 weeks.
- Published studies have not clearly established an anti-VEGF treatment standard
  - Approximately 90% of ophthalmologists use OCT alone or combined with FA and/or visual acuity as follow-up testing after anti-VEGF treatment to determine re-treatment.
- CATT
  - The Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) is comparing Lucentis with Avastin
  - CATT will also examine whether a reduced dosing schedule based on clinical response is as

effective as a fixed schedule of monthly injections.
    - Monthly surveillance will include OCT to monitor changes in subretinal and intraretinal fluid as well as fluorescein angiography to measure changes in lesion size.
    - The large, multicenter trial is not scheduled to be completed until 2011

B. VEGF TRAP-EYE

- VEGF Trap-Eye (Bayer HealthCare and Regeneron) is a new anti-VEGF drug for the treatment of wet AMD. It has successfully completed Phase 2 clinical trials (CLEAR-IT 2) and has entered the third and final stage of FDA-mandated clinical trials before becoming commercially available to patients.
- VEGF Trap-Eye is a receptor decoy with a higher affinity for VEGF than native VEGF receptors or any of the currently available anti-VEGF drugs. Unlike Macugen, Lucentis and Avastin, which all act through inhibition of VEGF-A, VEGF Trap binds all types of VEGF as well as the related placental growth factor.
- Results from the Phase 2 study were presented at the 2008 annual meeting of the Retina Society. Patients receiving monthly doses of VEGF Trap-Eye for 3 months followed by PRN dosing achieved mean improvements in visual acuity versus baseline of 9.0 letters and significant reduction of CNV lesion size.
- In the Phase 3 trials, VIEW 1 and VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet age related macular degeneration), the companies are evaluating VEGF Trap-Eye in direct comparison with Lucentis administered 0.5 mg every four weeks. Dosing schedules during the first year of the studies (following three monthly doses) is as follows:
    - 0.5 mg every 4 weeks
    - 2 mg every 4 weeks
    - 2 mg every 8 weeks
- PRN dosing will be evaluated during the second year of each study. The VIEW 1 study is currently enrolling patients in the United States and Canada and the VIEW 2 study is currently enrolling patients in Europe, Asia Pacific, Japan and Latin America.
- VEGF-Trap is administered by intravitreal injection, just like Lucentis and Avastin, but the advantage of this drug is that it lasts much longer. Early reports

are that it’s effects typically last for 3 months, compared to just 1 month for Lucentis.
- VEGF-Trap will probably be the first real competitor to Lucentis that is approved by the FDA for the treatment of wet AMD (Avastin is used off-label). Other drugs are in the pipeline, but VEGF-Trap is, to my knowledge, the only one currently in Phase 3.

C. Is there a benefit of late anti-VEGF therapy for wet AMD?

- Conflicting reports on the ability of Avastin to improve vision in patients with long-standing exudative AMD.
- In one paper, published by a group of researchers from Israel, we are informed that Avastin therapy can improve vision in patients with long-standing low vision secondary to wet AMD.
- Therefore, it may be beneficial to initiate anti-VEGF therapy in all suitable low vision patients regardless of how long they have endured the vision loss.
- Ehrlich R, et al. Outcome of bevacizumab (Avastin) injection in patients with age-related macular degeneration and low visual acuity. Retina 2008;28:1302-07.
- http://www.ncbi.nlm.nih.gov/pubmed/18664935

- In the second paper, published by a group of researchers from Austria, we are presented with exactly the opposite results.
- They found that vision did not significantly improve in patients that had advanced lesions that were fibrotic or had been previously treated by other means.
- Therefore, low vision patients with long-standing wet AMD would not be expected to benefit from anti-VEGF therapy.
- Krebs I, et al. Efficacy of intravitreal bevacizumab (Avastin) therapy for early and advanced neovascular age-related macular degeneration. Acta Ophthalmol. Epub 2008 Oct 17
- http://www.ncbi.nlm.nih.gov/pubmed/18937801

- The low vision management of patients with wet AMD has always involved maximizing the patient’s vision potential.

- Today, that should include a consultation with a retinal specialist who is prepared to initiate a trial of anti-VEGF therapy in suitable patients regardless of how long the disease has been present.
- With time, additional research may help us better target those patients most likely to benefit visually from late therapy of wet AMD.

2. GENETICS

A. Overview of AMD genetics

1. Genetic influence on AMD

First-degree relatives of patients with AMD, as compared with first-degree relatives in families without the disorder, are at increased risk (odds ratio, 2.4) for the condition, are affected at a younger age, and have an increased lifetime risk of late AMD (risk ratio, 4.2)

Polymorphisms in the complement factor H (CFH) and the LOC387715 genes have been associated with increased incidence of both wet and dry AMD. High risk variants also increases risk of progression.

2. Compliment Factor H

CFH is implicated in all stages of AMD (from early hallmarks such as drusen to vision-disabling late AMD) and both major subtypes (wet and dry).

The risk increases with each successive stage to an odds ratio of 11.0 for late AMD.

It was calculated that individuals homozygous for the CFH Y402H polymorphism have a 48% risk of developing late AMD by age 95 years while this risk does not exceed 22% for non-carriers.

Homozygous CFH Y402H carriers had a higher risk of bilateral than of unilateral late AMD

The association of both wet and dry AMD with CFH signifies a common pathogenesis involving the complement system.

CFH is an important regulator of the complement system.

CFH specifically inhibits the alternative complement cascade but also regulates the common pathway.

An aberration in the function or expression of the CFH protein could interfere with the essential downregulation of the alternative pathway and lead to excessive inflammation and damage of the tissue.

3. LOC387715

Research has identified the LOC387715 locus within chromosome 10q26 as a second major locus contributing to AMD pathogenesis

We have virtually no biological data to explain its potential role. (The function of this gene is unknown)

Rivera and co-workers found the strongest association over the LOC387715 gene conferring a 7.6-fold increased risk for individuals homozygous for SNP Ala69Ser.

The research indicate an independent contribution of the effects of risk alleles at the LOC387715 (Ala69Ser) and CFH (Tyr402His)-gene locus to the overall disease risk (Figure 2).

4. Factor B/complement component 2:

Factor B (BF) and complement component 2 (C2) genes are located 500 base pairs apart on chromosome 6p within the major histocompatibility complex class III region.

There was a common risk haplotype across BF and C2 (OR, 1.32), as well as two protective haplotypes (OR, 0.36, and 0.45, respectively)

Recent association of the complement component 2/factor B locus with ARM serves to strengthen the argument that we are dealing with the alternative complement pathway as a key pathogenic factor for ARM.

5. Gene-Gene Interaction (epistasis)

No significant interactions (epistasis) among five common variants at the three major loci (CFH, LOC387715, and C2-FB) have been found.

Specifically, a model in which the risk alleles at the three loci act independently (individual risks are multiplied to generate a combined risk profile) provided a better fit of the observed data than the same model with the inclusion of interlocus interference

6. Gene-Environment Interaction

No interaction between known genetic factors and smoking and diet have been proven.

7. Clinical Relevance

The clinical goals of genetics research for ARM are as follows:

(1) to identify the pathogenic mechanisms of the disease so that preventive therapies can be developed and

(2) to identify individuals at risk for developing ARM so that preventive therapies can be appropriately and cost-effectively implemented to lower the probability of developing disease.

Genetic studies have convincingly demonstrated that there exist common alleles of substantial effect on AMD pathogenesis.

The finding of such common alleles with substantial effects makes predictive DNA testing a tempting option although the mechanisms and thus the biological consequences conferred by the common risk alleles at the respective gene loci are not yet understood.

Consequently, the knowledge of being carrier of risk alleles is currently not matched by adequate options for preventive strategies or possible treatment modalities

By recognizing that a positive family history of ARM can significantly increase one’s risk of developing ARM, we can use this information to condition our recommendations for patients who show mild findings of ARM at an early age.

While one may hesitate to recommend vitamin and mineral supplementation for every patient with mild findings of ARM, one may want to consider recommending such supplements for those who have an increased genetic risk.

B. Complement factor H gene determines benefit of AREDS supplement on AMD progression

- Klein ML, et al. CFH and LOC387715/ARMS2 Genotypes and Treatment with Antioxidants and Zinc for Age-Related Macular Degeneration. Ophthalmology. 2008;115:1019-25.
- http://www.ncbi.nlm.nih.gov/pubmed/18423869
- A study finds that persons homozygous for the compliment factor H (CFH) high-risk allele (CC) have a smaller treatment response to the AREDS vitamin/mineral supplement than persons homozygous for the CFH low-risk allele (TT).
- A retrospective analysis was undertaken of 876 white participants in the AREDS study with categories 3 and 4 (high risk for progression) AMD.
    - The participants were genotyped for the SNP in the CFH (Y402H, rs1061170) and LOC387715 (A69S, rs10490924) genes.
    - Logistic regression analysis assessed interactions of these genotypes to determine the relationship between CFH and LOC387715 genotype and treatment response with antioxidants plus zinc, defined as progression from high-risk to advanced AMD.
- Progression occurred in 264 of 876.
    - The researchers found a treatment interaction between the CFH Y402H genotype and supplementation with antioxidants plus zinc (CC; P = 0.03).
    - A very strong interaction (P = 0.004) was observed in the AREDS treatment groups taking zinc when compared with the groups taking no zinc, but not in groups taking antioxidants compared with those taking no antioxidants (P = 0.59).
    - There were no significant treatment interactions observed with LOC387715.
- This study’s major finding was evidence of a possible interaction between CFH genotype and treatment with antioxidants plus zinc when compared with placebo.
    - Supplementation was associated with a greater reduction in AMD progression (68%) in those with

the low-risk TT genotype compared with those with the high-risk CC genotype (11%).
    - These results may imply that the strong genetic predisposition to AMD conferred by the CC genotype limits the benefits available from zinc and antioxidants.
- Further analysis of the data revealed that the genotype–treatment interaction is related primarily to the zinc component of the supplements.
    - Zinc is very effective in decreasing the risk of progression in persons without the CFH high-risk allele (60% reduction in progression rate in zinc vs no zinc) but there is little protection if the person is homozygous for the CFH high-risk allele (10% reduction).
    - An extensive literature implicates zinc as a key metal ion in immune and inflammatory processes. Whether zinc plays a direct or indirect role in complement factor H-mediated inhibition of inflammation remains unclear. It may be that the Y402H substitution alters these roles, resulting in the interaction noted between CFH genotype and oral supplementation with zinc.
- These results suggest that treatment response to AREDS-type supplements may be affected by an individual’s genotype.
    - The major benefit is seen in those individuals with the low-risk CFH genotype who could lower their rate of AMD progression by approximately two thirds.
    - AREDS-type supplements have less impact on those with the high-risk CFH genotype, although they still had an effect.
- The authors do not believe that their results justify routine genetic testing at this time. Although treatment effect may vary by CFH genotype, some benefit is derived by individuals in all CFH genotype groups, and no effective alternative interventions are currently available.
- In summary, it appears that an individual’s response to AREDS supplements may be related to CFH genotype.
    - This could have clinical relevance by predicting treatment outcome and potentially preventing unwanted side effects in those who may not benefit.

- This is among the first pharmacogenetic studies to suggest interaction between genotype and treatment.

1. FISH OIL

A. Meta-analysis of 9 studies: consumption of omega-3 fatty acids cuts risk of AMD

- Chong EWT, et al. Dietary omega-3 fatty acid and fish intake in the primary prevention of age-related macular degeneration: a systematic review and meta-analysis. Arch Ophthalmol. 2008;126:826-33.
- http://www.ncbi.nlm.nih.gov/pubmed/18541848
- A comprehensive review of the literature finds that consumption of foods rich in omega-3 fatty acids and fish intake twice or more per week may prevent AMD
  - The investigators considered randomized controlled trials (RCTs) and prospective cohort, case-control, and cross-sectional studies evaluating omega-3 fatty acid or fish intake from food or omega-3 fatty acid supplements in the primary prevention of AMD (ie, from no disease to early or late AMD).
  - They excluded studies in which participants already had early AMD, as these studies evaluated the role of omega-3 fatty acid and fish intake for secondary prevention (ie, progression of early to late AMD).
- Of 2754 abstracts identified, 3 prospective cohort, 3 case-control, and 3 cross-sectional studies met the criteria.
  - No RCTs met the inclusion criteria.
  - published literature up to May 2007
- Nine studies provided data on a total sample of 88,974 people, including 3203 AMD cases.

DIETARY OMEGA-3 FATTY ACID INTAKE AND EARLY AMD

- only 2 prospective cohort studies evaluated this
  - no pooled results
- Data from 2 prospective cohort studies, the Blue Mountains Eye Study (OR,0.41; 95% CI, 0.22-0.75) and the Nurses' Health Study and the Health Professional Follow-up Study (OR for DHA, 0.70; 95% CI, 0.52-

0.93)24 were consistent with a protective effect of omega-3 fatty acids for early AMD.

DIETARY OMEGA-3 FATTY ACID INTAKE AND LATE AMD

- One prospective cohort study and 3 case-control studies contributed to the pooled analysis.
- All 4 studies reported an inverse association, with 2 case-control studies reporting a statistically significant association between omega-3 fatty acid intake and late AMD.
- The pooled OR for late AMD comparing the highest with the lowest omega-3 fatty acid intake category was 0.62 (95% CI, 0.48-0.82).

FISH INTAKE AND EARLY AMD

- Three prospective cohort studies and 3 cross sectional studies contributed to the pooled analysis, with all studies reporting an inverse association
- only 1 cohort study reported a statistically significant association between fish intake and early AMD.
- The pooled OR for early AMD comparing the highest with the lowest fish intake category was 0.76 (95% CI, 0.64-0.90).
- Pooling results from only prospective studies, the OR increased to 0.63 (95% CI, 0.50-0.80).

FISH INTAKE AND LATE AMD

- One prospective cohort study, 3 case-control studies, and 2 cross-sectional studies contributed to the pooled analysis.
- All studies reported an inverse association
- The pooled OR for late AMD comparing participants in the highest with those in the lowest fish-intake category was 0.67 (95% CI, 0.53-0.85).

- Results from metaanalysis showed that consumption of fish twice or more per week and foods rich in omega-3 fatty acids was associated with a reduced risk of both early and late AMD.
- Omega-3 fatty acid intake, comparing the highest with the lowest intake category, was associated with a 38% reduction in the likelihood of late AMD.

- Fish intake of twice or more per week compared with an intake less than once per month was similarly associated with a 37% reduction in risk of early AMD
- Fish intake was also associated with a protective effect on the risk of late AMD (pooled OR, 0.67).
- Our findings are supported by a strong underlying biological rationale.
    - Docosahexaenoic acid in particular is an essential structural component of the retinal membranes and is found in the highest concentration per unit area in the retina.
    - The outer photoreceptor-cell segments of the retina are constantly shed in the normal visual cycle and deficiency of this omega-3 fatty acid may initiate AMD.
    - There is also evidence that such long-chain omega-3 fatty acids protect against oxygenic, inflammatory, and age-associated pathology of the vascular and neural retina, which are possible pathogenic factors for AMD development.
- We found highly statistically significant pooled estimates, but owing to inherent biases from some of the studies additional prospective data, especially from RCTs, are warranted.
    - Although AREDS2, a large RCT, evaluating omega-3 fatty acid (EPA and DHA) and/or carotenoid (lutein and zeaxanthin) supplement intake compared with placebo has started recruitment, it will evaluate their roles in the secondary prevention of AMD (ie, progression from early to late AMD).
    - Hence observational studies, particularly prospective cohort studies, provide the best available evidence regarding these dietary factors for the primary prevention of AMD
- In conclusion, these results suggest that high dietary intakes of omega-3 fatty acids and fish are associated with a reduced risk of both early and late AMD.
- Routine recommendation of omega-3 fatty acid and fish intake for AMD prevention is not warranted until additional information from prospective studies and RCTs emerges.

B. European population-based: Oily fish once-per-week cuts risk of wet AMD

- Augood C, et al. Oily fish consumption, dietary docosahexaenoic acid and eicosapentaenoic acid intakes, and associations with neovascular age-related macular degeneration. Am J Clin Nutr. 2008;88:398-406.
- http://www.ncbi.nlm.nih.gov/pubmed/18689376
- A European population-based survey finds that eating oily fish at least once per week compared with less than once per week was associated with cutting the risk of developing neovascular AMD (NV-AMD) in half.
- Participants aged 65 or older in the cross-sectional population-based EUREYE study underwent fundus photography and were interviewed by using a food-frequency questionnaire.
    - EUREYE was a multi-centre community prevalence study in 4760 people aged 65 years and over in seven European communities.
    - The study is designed to establish the prevalence of AMD, to measure the impact of AMD on vision-related quality of life, and to identify possible risk factors.
- Dietary intake data and fundus images were available for 105 cases with NV-AMD and for 2170 controls without any features of early or late AMD.
- Eating oily fish at least once per week compared with less than once per week was associated with a halving of the odds of NV-AMD (OR = 0.47).
- Compared with the lowest quartile, there was a significant trend for decreased odds with increasing quartiles of either DHA or EPA.
    - ORs in the highest quartiles were 0.32 for DHA and 0.29 for EPA.
- The investigators conclude that eating oily fish at least once per week compared with less than once per week was associated with a halving of the OR for NV-AMD.

C. AREDS: fish oil consumption decreases the risk of progression to advanced stages of both wet and dry AMD

- SanGiovanni JP, et al. Omega-3 long-chain polyunsaturated fatty acidintake inversely associated with 12-year progression to advanced age-related macular degeneration. Arch Ophthalmol. 2009;127:110-2.
- http://www.ncbi.nlm.nih.gov/pubmed/19139352
- A new research report from the AREDS study finds that fish oil consumption decreases the risk of progression

to advanced stages of both wet and dry AMD over a 12-year follow-up period.

- The Age-Related Eye Disease Study (AREDS) was a study designed to assess the clinical course, prognosis, and risk factors of AMD.
  - AREDS examined the relationship of dietary intake of omega-3 long-chain polyunsaturated fatty acids (fish oil) with progression to advanced AMD in 1837 participants. Dietary intake was estimated with questionnaire.
- Participants reporting the highest consumption of fish oil were approximately 30% less likely than their peers reporting the lowest fish oil consumption to develop advanced AMD.
  - Results for geographic atrophy and neovascular AMD were similar.
- The researchers conclude that because the concentration of omega-3 long-chain polyunsaturated fatty acids in the retina is dependent on dietary composition, these nutrients may represent an easily implemented approach to decreasing the risk of AMD progression.
- This is additional evidence that points to omega-3 consumption as a safe and effective means of decreasing the risk of progression for all patients with AMD.
- Unlike the AREDS vitamin/mineral supplement -- which is only effective for a narrow range of patients with AMD, has the potential for undesirable side effects, and is contraindicated for smokers – fish oil consumption has no serious adverse effects and appears to be effective in slowing the progression of AMD for a broad range of persons with the disease.
- We will have to await the results of AREDS2 to have a prospective, interventional, randomized clinical trial to prove the benefit of fish oil for AMD. But the existing evidence is strong enough to have me recommend fish oil for all my AMD patients.