DISEASE OF THE MACULA

From the 6th Annual Retina Symposium: Medical and Surgical Retina Update, presented by the Illinois Eye and Ear Infirmary

Age-related Macular Degeneration

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Theories of development of age-related macular degeneration (AMD): diet, environment, and genetic predisposition involved; nutrition—diet shown to play role in Beaver Dam Eye Study, Rotterdam Eye Study, Blue Mountains Eye Study, and Barbados Eye Study; frequency of AMD low in women in Japan, higher in men and women in the United States

Risk factors: age (AMD seen in 30% of individuals age >75 yr); smoking (increases risk 2- to 3-fold); family history (1 relative with AMD increases risk from 12% to 50%); body mass index (BMI; if ≥30, risk increases 2.5 times); dietary intake of fish and nuts protective

Age-Related Eye Disease Study (AREDS) 1: cocktail of β-carotene, vitamins C and E, zinc, and copper given to 3600 participants; β-carotene precursor to pigmentary molecules in retina; results—cocktail decreased risk from 28% to 21% (absolute reduction of 7%); development of advanced AMD reduced by 25%; progression to wet AMD in patients with categories 3 or 4 disease reduced by 34%; moderate vision loss (15 letters) reduced by 19%

Age-Related Eye Disease Study (AREDS) 2: lutein represents 36% of retinal carotenoids; more lutein present in blood; zeaxanthin more concentrated in fovea; meso-zeaxanthin found only in central fovea; omega-3 fatty acids (FAs)—active in cellular membranes; important for visual function; types include docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA); reduce endothelial growth factor and activate tyrosine kinase receptor

Carotenoids in Age-Related Eye Disease Study: enrolled 38,000 women without AMD; women with high consumption of DHA and EPA had 0.62 to 0.66 relative risk (RR) of developing AMD; consumption of fish ≥1 times per week reduced RR to 0.58; evaluation of fundus photographs for 1700 women showed diet high (above 78th percentile) in lutein and zeaxanthin protective at ages <75 yr with odds ratio (OR) of 0.57 for intermediate drusen; intake of polyunsaturated FAs and ratio of omega-6 (longer chain) to omega-3 forms also important

Age-Related Eye Disease Study (AREDS) 2 outcome: risk for progression to advanced AMD decreased with oral supplements of 10 mg lutein, 2 mg zeaxanthin, 350 mg DHA, and 650 mg EPA [results recently published; AREDS 2 Research Group, 2013]

Other vitamins: C and E — study found no decrease in vision loss after 8 yr among 14,236 male physicians >50 yr of age given supplemental vitamins C (500 mg/day) and E (400 IU every other day); vitamin D — suppresses inflammation at retinal pigment epithelium (RPE); inhibits angiogenesis in cultured endothelial cells; study found high concentrations of vitamin D protective in postmenopausal women age <75 yr; OR of pigmentary changes in fovea decreased by 57%; OR of large drusen <1 (not statistically significant); inverse relationship between vitamin D and AMD observed, regardless of carotenoid intake

Genetics: smoking and genetic risk — smokers have OR of 1.29 for development of AMD; smokers with polymorphism in complement factor (CFH) have OR of 2.4; smokers homozygous for CFH polymorphism have OR of 34; case control study of 450 individuals showed homozygosity for alleles in both CFH and LOC increased risk for AMD 50-fold; genotype and AREDS supplements — response of individual to AREDS supplements possibly related to genotype; genetic tests — speaker recommends against genetic testing; Comparison of AMD Treatments Trials (CATT) genotyped 1100 (834 treated) patients for all alleles found no differences in response to treatment

Recommendations for patients: reduce smoking, reduce obesity, exercise (3 times per week reduces risk for exudative AMD); caution about overuse of vitamins

New approaches: inadequate data available for resveratrol, astaxanthin, and other new agents; ForeSee home monitoring device to detect distortions of fovea and hyperacuity in phase III trials; Digisight Technologies works over phone; retinal rejuvenation therapy in development using short microbursts with laser to dry drusen; MacuClear; brimonidine for neuroprotection; anti-inflammatory agents, e.g., sirolimus (rapamycin)

Angiogenesis

Peter Campochiaro, MD, Eccles Professor of Ophthalmology and Neuroscience, Retina Division, The Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, MD

Categories: ischemic retinopathies—e.g., diabetic retinopathy, retinal vein occlusion, and retinopathy of prematurity; cause

Educational Objectives

The goal of this program is to improve the prevention and treatment of macular disease. After hearing and assimilating this program, the clinician will be better able to:

1. Recommend appropriate dietary supplements and changes in lifestyle to reduce the risk of developing age-related macular degeneration (AMD).
2. Elaborate on the various research models for AMD and the results of different treatments in these models.
3. Summarize the soluble and insoluble factors important for the development of AMD.
4. Evaluate the data from the various clinical trials testing different dosing algorithms for treatment of AMD with anti-vascular endothelial growth factor (VEGF) agents.
5. Balance considerations of efficacy and treatment burden when prescribing the dosing regimen for anti-VEGF agents.

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio-Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, the following has been disclosed:

Dr. Campochiaro is an advisor and consultant for Advanced Cell Technology, Aerpio Therapeutics, Elan Corporation, Gene Signal, Genentech, GlaxoSmithKline, Norvox, and Regeneron Pharmaceuticals; he also receives grant/research support from Genentech, Genzyme, GlaxoSmithKline, and Oxford BioMedica. Dr. Lim is on the advisory boards for GlaxoSmithKline and Regeneron Pharmaceuticals, is a consultant for Thrombogenics, is on the data monitoring committee for Quark Pharmaceuticals, receives grant support from Regeneron Pharmaceuticals, and is a Speaker for Genentech and Regeneron Pharmaceuticals. Dr. Ulanski and the planning committee reported nothing to disclose. In their lectures, Drs. Campochiaro and Lim present information that is related to the off-label or investigational use of a therapy, product, or device.
Research models: ischemic retinopathies—vascular endothelial growth factor (VEGF) involved in development of retinal vessels; exposure of mice to oxygen soon after birth causes downregulation of expression of VEGF; development of blood vessels stops and new vessels regress; causes areas of ischemia, increase in VEGF, and NV; CNV—laser rupture of BM causes growth of blood vessels through BM and spread of hypofluorescence typical of CNV; vessels come from choroid through BM to network of vessels beneath retina; to visualize, perfuse mice with fluorescein-labeled dextran and quantitate with choroidal flat mount; RAP—transgenic mice with expression of VEGF and photoreceptors show proliferation of endothelial cells from deep capillary bed that grow down into photoreceptors, with growth and proliferation of blood vessels in subretinal space; appearance same as that of CNV by fluorescein angiography (hypofluorescent spots beneath retina); additional model—mice with inducible expression of VEGF in retina; mice remain normal if untreated; administration of doxycycline to stimulate late expression of VEGF causes NV; expression higher than that in mice with constitutive expression of VEGF; causes exuberant NV and profuse leakage, resulting in exudative detachments.

Anti-VEGF treatment: standard of care; in models, ablifercept causes marked suppression of CNV; Investigation of Efficacy and Safety in Wet AMD (VIEW) 1 and 2 trials showed ablifercept given at 0.5 mg every month or 2 mg every 2 mo equivalent to ranibizumab (RBZ) at 0.5 mg every month.

Platelet-derived growth factor (PDGF)-BB: upregulated by hypoxia; designed ankynin repeat protein (DARP) blocks PDGF-B and suppresses CNV; anti-VEGF DARP alone also suppresses CNV; blocking PDGF-BB alone shows some efficacy; blocking VEGF more efficacious; blocking both with anti-PDGF (Fovista) plus anti-VEGF shows additive effect in trials; in inducible model, exudative detachments suppressed by treatment with anti-PDGF plus anti-VEGF; anti-PDGF alone does not suppress; anti-VEGF alone suppresses slightly.

Stromal-derived factor (SDF): SDF-1 recruits bone marrow-derived cells (BMDCs) into retina; in ischemic retinopathy model, mice show higher levels of SDF-1 and transient increase in CXCR4 (receptor for SDF-1) after exposure to oxygen; double transgenic mice with increased expression of VEGF also have increased CXCR4 and SDF-1; mice with no ischemia have no increase in SDF-1; glial cells stained by glial fibrillary acidic protein (GFAP) in ischemic mice express increased SDF-1 that recruits BMDCs causing increase in CXCR4 in ischemic retina; BMDCs (ie, macrophages) accumulate around regressing blood vessels, hyaloid vasculature, and buds of NV; 3 antagonists of CXCR4 suppress CNV; in ischemic retinopathy model, ischemia increases number of BMDCs; increase suppressed by CXCR4 antagonists.

Hypoxia-inducible factor 1 (HIF-1): transcription factor responsible for hypoxia-induced upregulation of VEGF-A, PDGF-BB, and SDF-1; HIF-1 degraded under normoxic conditions; cardiac glycosides suppress transcription of HIF-1 in ischemic retinopathy model; digoxin—suppresses all genes regulated by HIF-1, eg, SDF-1 and receptor, VEGF and receptor, scatter factor, placental growth factor, PDGF-B, and angiotatin (ANG)-2; intraperitoneal injection inhibits all RNV in ischemic retinopathy model; intracocular injection also suppresses retinal NV, reduces influx of BMDCs, and suppresses CNV; doxorubicin— injection of nanoparticles containing doxorubicin into mouse eyes suppresses RNV and CNV for ≥2 mo and causes regression of NV by blocking multiple pathways (also seen in Fovista trial); CNV and upregulation of HIF-1 apparently caused by oxidative stress (major underlying cause).

Integrins: bind to extracellular matrix (ECM) and transmit signals to cells; integrins α5β1 and α2β3 normally not present on endothelial cells in retina but upregulated during angiogenic processes; endothelial cells participating in CNV stain for α5β1; antagonist causes suppression and regression of NV.

Tie receptors: occur only on endothelial cells; Ang-1 agonist for Tie receptors; Ang-2 antagonist; binding of Ang-1 to Tie2 stimulates phosphorylation of receptor and downstream signaling of several molecules (eg, nitrous oxide, Akt); binding of Ang-2 suppresses binding of Ang-1 and prevents signal; in ischemic retinopathy model, Ang-1 does not change but Ang-2 increases with increasing duration of ischemia; expression during retinal vascular development, Ang-2 expressed first at surface of retina then deep as vessels develop; in adult animals, some expression continues along deep capillary bed; hypoxia causes ectopic expression of Ang-2 in association with blood vessels; normal expression in adult animals seen in horizontal cells because of their proximity to deep capillary bed; knock-out of Ang-2 abrogates retinal vascular development; effect of VEGF—in ischemic retinopathy model (high levels of VEGF), overexpression of Ang-2 causes increased NV; overexpression of Ang-2 in presence of low levels of VEGF (1 wk later) causes regression of NV; similar effect seen in CNV; effect of Ang-2 depends on context; expression of Ang-1 suppresses NV regardless of context; because Tie2 controls all input from ECM, blockade by Ang-2 makes soluble factors more important.

Vascular endothelial protein tyrosine phosphatase (VEPTP): another control mechanism on Tie2 pathway that inhibits Tie2 signaling; expression—increased by hypoxia; little expression seen in normoxic retina; expressed in ischemic retinopathy model, especially in buds of NV; effects— injection of antibody against VEPTP suppresses RNV; NV in VEGF transgenic mice, and CNV; treatment with small molecule inhibitor of VEPTP blocks NV and leakage (no expression of albumin around NV buds) in mice.

Anti-VEGF Treatment

Jennifer I. Lim, MD, Professor of Ophthalmology and Director of the Retinal Service, University of Illinois Eye and Ear Infirmary, Chicago

Monthly dosing: Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (Anchor) and Minimally Classic Occult Trial of the Anti-VEGF Antibody RBZ in the Treatment of Neovascular AMD (MARINA) trials showed monthly injection in patients with NV AMD produces gain of 9 to 11 letters after 1 yr (effect sustained for 2 yr).

Quarterly dosing: Randomized, Double-masked, Sham-controlled Trial of RBZ for Neovascular AMD (PIER) study showed fixed dosing monthly for 3 mo followed by quarterly injections produced decline in visual acuity (VA); Efficacy and Safety of Monthly versus Quarterly RBZ Treatment in Neovascular AMD (EXCITE) study also showed quarterly dosing after 3 monthly doses inferior to monthly dosing.

As-needed dosing with less than monthly follow-up: Open-label Extension Trial of RBZ for Choroidal Neovascularization Secondary to AMD (HORIZON) study found visual acuity (VA) dropped from gain of 9 letters to 2 letters after 2 yr of prn dosing; patients initially followed up only every 6 mo; protocol subsequently changed to follow-up every 3 mo; Safety Assessment of Intravitreal Lucentis for AMD (SAILOR) study evaluated 3 monthly doses then quarterly prn; found results inferior (2 letters gained) to those with monthly dosing.

As-needed dosing with monthly follow-up: Prospective Optical Coherence Tomography (OCT) Imaging of Patients with Neovascular AMD Treated with Intravitreal RBZ (PONTO) Study used 3 monthly injections, then monthly follow-up with re injection if ≥5 letters lost or central retinal thickness (CRT) increased ≥100 μm; results similar to those in ANCHOR and MARINA; Study of RBZ in Patients with Subfoveal Choroidal Neovascularization Secondary to AMD (SUSTAIN) found average gain of ≥6 letters after 3 initial treatments; gain fell to ≤4 letters after switch to prn dosing; only 3 additional injections given over 9 mo; SUSTAIN found that CRT decreased after first 3 injections by ≥101 μm but by only 91 μm after
12 mo of pm dosing (monthly follow-up); CATT and Study of RBZ Administered Monthly or on an As-needed Basis in Patients with Subfoveal AMD (HARBOR) showed results of monthly follow-up and pm dosing close to those of monthly regimen

**CATT study:** ≥1,200 patients treated with either RBZ or bevacizumab (BVZ) either monthly or pm with monthly follow-up; found VA similar for pm and monthly dosing with each drug (2-letter difference); OCT results best for RBZ monthly, slightly less robust for RBZ given PRN and BVZ given PRN; VA and OCT results declined at yr 2 with pm dosing

**HARBOR:** compared 0.5-mg or 2-mg dose of RBZ given monthly or pm; at 2 yr, no difference seen between doses or between monthly vs pm dosing with monthly follow-up (9 letters gained with monthly vs 8 pm); pm dosing now approved for RBZ

**Treat-and-extend:** treat, extend interval, decrease interval if leakage recurs; reduces treatment burden, number of visits, and number of injections, with no macular hemorrhages or decline in VA [Spaide R et al, 2007]; retrospective study showed gain of 11 letters vs 2 with PRN dosing [Oubraham H et al, 2011]; study with treatment-naïve eyes found gains in VA equivalent (=10 letters) with both RBZ and BVZ; 6 to 8 injections needed per year

**VIEW 1 and 2:** evaluated dosing monthly vs every 2 mo (no difference in outcome in first year); after 1 yr, gave capped dosing (injection every 3 mo if no injection given recently); results equivalent (33% gained ≥3 lines after 1 yr); no clinically relevant difference seen in VAs or OCT fluid results among RBZ monthly, aflibercept monthly, and aflibercept every 2 mo; with all drugs, monthly follow-up key, as is zero tolerance for recurrence of retinal fluid or intraretinal edema

### Acknowledgements

Drs. Ulanski, Campochiaro, and Lim spoke at the 6th Annual Retina Symposium: Medical and Surgical Retina Update, held March 22, 2013, in Chicago, IL, and presented by Illinois Eye and Ear Infirmary and the University of Illinois Department of Ophthalmology and Visual Sciences (to learn more about CME activities from the Illinois Eye and Ear Infirmary, please visit chicago.medicine.uic.edu). The Audio-Digest Foundation thanks the speakers and the sponsors for their cooperation in the production of this program.

### Suggested Reading


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- Review Educational Objectives on page 1: 5 minutes
- Take pretest: 10 minutes
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- Review written summary and suggested readings: 35 minutes
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DISEASE OF THE MACULA

1. Smoking increases the risk of developing age-related macular degeneration (AMD) by _____ and body mass index ≥30 increases it by _____.
   (A) 30- to 40-fold; 15 times  (B) 20- to 30-fold; 10 times  
   (C) 10- to 20-fold; 5 times  (D) 2- to 3-fold; 2.5 times

2. Choose the correct statements about the effects of diet on the risk for AMD.
   1. A cocktail of β-carotene, vitamins C and E, zinc, and copper produced an absolute reduction of 7% in risk for development of AMD
   2. A study found that consumption of fish ≥1 times per week reduced the relative risk to 0.58
   3. A study found that the ratio of omega-6 (longer chain) to omega-3 fatty acids is important
   4. A study found that supplemental vitamins C (500 mg/day) and E (400 IU every other day) was protective against vision loss in male physicians.
   5. A study found high concentrations of vitamin D were protective in postmenopausal women aged <75 yr
   (A) 2,3,4,5  (B) 1,2,3,4  (C) 1,2,3,5  (D) 1,3,4,5

3. A polymorphism in complement factor H has been shown to increase the odds of developing AMD among smokers.
   (A) True  (B) False

4. All the following have been demonstrated in mouse models of angiogenesis, except:
   (A) Exposure of mice to oxygen soon after birth causes downregulation of expression of vascular endothelial growth factor (VEGF)
   (B) Laser rupture of Bruch membrane in mice produces a condition similar to choroidal neovascularization (CNV) in humans
   (C) Transgenic mice that express VEGF show a condition similar to retinal angiomatous proliferation
   (D) Stimulation of expression of VEGF in mice causes regression of new blood vessels

5. Which of the following has been shown to suppress CNV?
   (A) Placental growth factor  (B) Designed ankyrin repeat protein  
   (C) Stromal derived factor  (D) Hypoxia-inducible factor 1

6. Three antagonists of the CXCR4 receptor for stromal derived factor 1 have been shown to suppress CNV in mouse models.
   (A) True  (B) False

7. Choose the correct statements about the role of the Tie2 pathway in neovascularization.
   1. In an ischemic retinopathy model, levels of angiopoietin (Ang)-2 increase with increasing duration of ischemia
   2. Ang-2 stimulates signaling through the Tie2 receptor
   3. Hypoxia causes ectopic expression of Ang-2 in association with blood vessels
   4. The effect of Ang-2 on NV depends on whether levels of VEGF are high or low
   5. Injection of antibody against vascular endothelial protein tyrosine phosphatase (VEPTP) suppresses retinal NV and CNV in mice
   (A) 1,2,3,4  (B) 2,3,4,5  (C) 1,3,4,5  (D) 1,2,4,5

8. Clinical trials have shown that giving patients with neovascular AMD monthly injections of ranibizumab produces gains in visual acuity of _____ letters after 1 yr
   (A) 2 to 3  (B) 4 to 5  (C) 9 to 11  (D) <2

9. The HORIZON study found that as-needed (prn) dosing of RBZ with follow-up visits every 6 mo was _____ to monthly injections.
   (A) Inferior to  (B) Equivalent to  (C) Superior to

10. Which of the following treatment algorithms was approved for treatment of AMD with RBZ on the basis of the results of the HARBOR trial?
    (A) Quarterly dosing  (B) Treat and extend algorithm  
    (C) prn with monthly follow-up  (D) None of the above