EXPLORING THE RETINA

Age-related Macular Degeneration

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Macular degeneration: leading cause of severe loss of vision in persons >50 yr of age in developed world; has nonneovascular (dry) and neovascular (wet) stages; wet form found in 10% to 20% of patients with age-related macular degeneration (AMD) but accounts for 90% of vision loss from AMD

Clinical manifestations: drusen first sign of AMD; drusen deposits under retina near macula; retinal pigment epithelium (RPE) near drusen may be destroyed; end stage characterized by atrophy of RPE, choroidal neovascularization (CNV), and scarring

Histopathology: early signs — before drusen visible, early diffuse thickening of Bruch membrane (BM) caused by accumulation of basal linear and basal laminar deposits; drusen nodular excrescences of thickened Bruch membrane, composed of protein and lipid components from RPE, neuroretina, choriocapillaris, and extracellular sources; diffusely thickened BM interferes with flow of nutrients between choroid and RPE, affecting function of neurosensory retina; hard drusen small and soft drusen large; progression of dry AMD — discrete atrophy of RPE observed; geographic atrophy refers to larger zones of RPE dropout with atrophy of choriocapillaris and degradation of photoreceptors; transformation to wet AMD — occurs as abnormal vessels (usually from choriocapillaris) break through diseased BM to invade subretinal space; vessels incompetent and leaky, and produce exudates of fluid, lipid, or blood; influx of inflammatory cells may lead to subretinal fibrosis

Clinical staging: drusen may be small (<63 μ in diameter), intermediate (63-124 μ), or large (>125 μ); early AMD (Age-related Eye Disease Study [AREDS] category 2) characterized by small drusen and usually asymptomatic; intermediate stage (AREDS category 3) characterized by ≥1 large drusen and numerous medium-sized drusen; visual impairment usually mild; advanced AMD refers to presence of geographic atrophy affecting visual acuity or neovascularization (NV)

Symptoms: may include reduced central vision, central scotoma, metamorphopsia, decreased contrast sensitivity, and decreased color vision; symptoms more acute in neovascular stage

Risk factors: age, family history, sex, genetic factors, ethnicity, smoking, high cholesterol, hypertension, cardiovascular disease, and low intake of antioxidants and lutein; advancing age greatest risk factor; smoking strongest modifiable risk factor

Age-related Eye Disease Study: placebo-controlled, 4-arm study in >3600 patients with AMD assessed antioxidants, zinc (Zn), and combination of antioxidants plus Zn; supplements significantly reduced progression to advanced AMD; combination group had best outcomes; progression to advanced AMD occurred in 28% of placebo group and 20% of combination group; antioxidants included 500 mg vitamin C, 400 IU vitamin E, and 15 mg β-carotene; Zn arm received 80 mg Zn and 2 mg copper; combination of these (original AREDS formula) initially recommended for patients with category 3 and 4 AMD

AREDS2: tested benefits of lutein, zeaxanthin, and ω-3 fatty acids in >4200 patients; compared AREDS formula with various modifications that could include 10 mg lutein, 2 mg zeaxanthin, and 1 g ω-3 fatty acids; no differences seen among arms; although no modification of formula conferred additional benefit, concerns about increased risks from β-carotene in smokers led to new formula that substituted lutein and zeaxanthin for β-carotene

Management of dry AMD: patients >60 yr of age should have annual surveillance and avoid smoking; no evidence supports supplements for early AMD; patients with intermediate AMD should self-monitor vision, be examined every 6 to 12 mo, and undergo fluorescein angiography (FA) or optical coherence tomography (OCT) if NV suspected; patients should take AREDS or AREDS2 supplements; smokers should avoid β-carotene; no effective treatments available; therapies that inhibit complement and alter visual cycle are being tested; for severe disease, stem cell therapy being tested

Management of neovascular AMD: patients with drusen and exudates should be tested for NV using FA or OCT; FA — detects size, location, type, and leakage of neovascular lesions; identifies forms of neovascular AMD including classic CNV, occult CNV, mixed patterns, retinal angiomatous proliferation, and idiopathic polypoidal choroidal vasculopathy (PCV); indocyanine green (ICG) helpful for diagnosing PCV; OCT — used to diagnose and follow response to treatment; may show fluid under RPE (pigment epithelial detachment) or neurosensory retina (subretinal fluid); or intra-retinal fluid (cystic edema or thickening of neurosensory retina); interventions — laser photocoagulation (LPC) older treatment; photodynamic therapy (PDT) introduced in 2000; antivascular endothelial growth factor (anti-VEGF) agents introduced in 2006

Educational Objectives

The goals of this program are to improve diagnosis and treatment of retinal diseases. After hearing and assimilating this program, the clinician will be better able to:

1. Recognize risk factors for and signs of age-related macular degeneration (AMD).
2. Review the evidence supporting nutritional supplementation in patients with AMD.
3. Compare antibodies and treatment regimens used for AMD.
4. Assess the risks and benefits of using scatter laser for patients with retinal vein occlusion.
5. Interpret findings on fluorescence angiography and optical coherence tomography in patients with central serous chorioretinopathy.

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. Regillo is a consultant for and receives grant/research support from Genentech (a member of the Roche Group) and Regeneron Pharmaceuticals. Dr. Kim is a consultant for Alimera Sciences, Allergan, Bayer AG, and Novartis AG. The planning committee reported nothing to disclose. In his lecture, Dr. Regillo presents information related to the off-label or investigational use of a therapy, product, or device. In her lecture (Ultra-wide Field Imaging), Dr. Kim presents information related to the off-label or investigational use of a therapy, product, or device. In her lecture (Management of Chronic Serous Chorioretinopathy), Dr. Kim presents information related to the off-label or investigational use of a therapy, product, or device.
Laser photoocoagulation: rarely used; most effective if neovascular complex ≥200 μ from center of fovea; recurrence rates 50% to 70%; occasionally used for small peripapillary lesions; laser too destructive for treating subfoveal NV (present at time of diagnosis in >90% of patients with new-onset wet AMD)

Photodynamic therapy: nondestructive combination of laser and photosensitizing agent (eg, verteporfin); nondestructive light activates dye collected in neovascular complex and selectively occludes neovascular complex, with little damage to surrounding tissues; repeated every 3 mo until NV stops growing and leaking; eyes treated with PDT have less vision loss than those treated with placebo; most effective for classic NV; does not improve visual acuity; occasionally used in combination with anti-VEGF treatment

Anti-VEGF agents include aptamers, antibodies, and fusion proteins; VEGF family of glycoproteins secreted by cells in response to local hypoxia and ischemia; VEGF proteins induce angiogenesis and vascular permeability; agents bind freely difusible VEGF and block interaction with receptors on endothelial cells to prevent replication and leakage

Pegaptanib: oligonucleotide aptamer that blocks VEGF165 isoform; injected intravitreally every 6 wk; in phase III study, patients treated with pegaptanib had less vision loss than those receiving usual care (including PDT); mean visual acuity did not improve; agent replaced by newer antibodies including ranibizumab (anti-VEGF antibody fragment) and bevacizumab (antibody to VEGF); ranibizumab approved for treatment of wet AMD; bevacizumab used off label; these agents more broad spectrum and effective than pegaptanib

Ranibizumab: associated with improvements in visual acuity; phase III studies — MARINA compared ranibizumab with sham injection for treatment of minimally classic and occult neovascular AMD; ANCHOR compared ranibizumab with PDT in patients with classic CNV; in both trials, monthly ranibizumab associated with significant gains in visual acuity, compared with controls; subsequent studies aimed at reducing frequency of treatment did not demonstrate same visual gains, so individualized therapy now being explored; PrONT0 study — evaluated efficacy of as-needed treatment; gains in visual acuity comparable to those observed in pivotal studies; fewer mean injections required

Treatment regimens: in induction phase, 2 to 4 injections required every 4 to 5 wk to dry out macula; in maintenance phase, “treat and extend” approach used (times between treatments vary); Comparison of AMD Treatments Trials (CATT) conducted in United States and Inhibition of VEGF in Age-related CNV (IVAN) conducted abroad; both studies used 4-arm factorial design to evaluate monthly vs as-needed therapy and bevacizumab vs ranibizumab; CATT enrolled 1200 patients; agents performed similarly, but at 2 yr, outcomes inferior in as-needed arms; findings led to evaluation of treat-and-extend approach in studies of treat-and-extend show favorable outcomes in visual acuity with fewer treatments; anti-VEGF agents not curative, so ongoing therapy needed

Afibercept: pan-VEGF A blocker; VIEW 1 and VIEW 2 studies evaluated monthly treatment with afibercept vs ranibizumab and assessed use of afibercept every 8 wk for maintenance; afibercept equivalent to ranibizumab; dosing regimens of afibercept equivalent to one another and to ranibizumab regimen; afibercept may have longer duration of effect than ranibizumab or bevacizumab and may necessitate slightly fewer treatments

Summary: treatment regimens with anti-VEGF agents typically used as needed or in treat-and-extend protocol; close follow-up required; long-term therapy permits control but not cure; outcomes better when CNV treated early; patients with dry AMD should monitor vision at home; other growth factor inhibitors and complementary therapies being explored

Rationale: adaptive optics allow examination of individual rods and cones; wide-field imaging permits comprehensive view

Case 1: 21-yr-old woman presented with loss of vision; patient had vitritis, multiple white spots, hemorrhages, and cotton wool spots; antinuclear antibodies significantly elevated in this patient with lupus retinopathy; improved after 10-day course of steroids

Case 2: 34-yr-old man had vision loss to 20/60 in left eye, vitritis, and peripheral changes; diagnosis acute retinal necrosis; despite treatment with intravenous acyclovir, high-dose oral valacyclovir (Valtrex), and intravitreal ganciclovir, patient had no improvement and developed peripheral retina occlusion manifested by whitening in inferior half of macula and increased peripapillary hemorrhages; vision improved from 20/400 to 20/40 after vitrectomy to decrease load of cytokines and peripheral treatment with laser; ultrawide color photographs document such conditions; ultra-wide autofluorescence shows periphery

Case 3: ultra-wide field fluorescein angiography (UWFA) useful for examining patient with diabetic retinopathy, NV in periphery, ischemia, and microaneurysms

Case 4: patient with 7-field Early Treatment Diabetic Retinopathy Study photographs of fundus showed minimal peripheral findings, but UWFA revealed proliferative disease

Case 5: in 2 patients with same ischemia score, UWFA revealed that only one had NV; correct classification permits proper prognosis and treatment; patients with retinal ischemia 4 times as likely to develop diabetic macular edema

Pathophysiology: peripheral retinal ischemia increases production of VEGF, which increases macular edema and possibly NV; UWFA may allow surgeon to target areas of ischemia

Case 6: 83-yr-old with macular edema presented with decreased vision (20/80) in right eye; FA and OCT showed branched retinal vein occlusion; problem recurred after 8 injections of ranibizumab; UWFA showed areas of peripheral ischemia; macular edema resolved after treatment with laser

Scatter laser: VEGF levels elevated in venous occlusion and active diabetic retinopathy; REVOLUTION study — assessed whether treatment with scatter laser could improve vision and reduce number of injections of ranibizumab needed in patients with branched retinal vein occlusion; visual acuity similar in ranibizumab and ranibizumab plus laser groups, but less recurrent macular edema seen in laser group; patients with hemiretinal or central retinal vein occlusion may have widespread peripheral ischemia; findings of other studies — scatter laser treatment not effective in patients with chronic central retinal vein occlusion in small study; in another study, treatment with laser produced favorable outcomes in patients with less advanced disease, but results did not reach statistical significance

Management of Chronic Serous Chorioretinopathy

Dr. Kim

Etiology: central serous chorioretinopathy (CSC) associated with stress and competitive “type A” personality; stress may affect hypothalamic-pituitary-adrenal axis and increase secretion of glucocorticoids; systemic causes of CSC include transplantation of bone marrow or solid organs, lupus erythematosus, membranoproliferative glomerulonephritis type 2, infection with Helicobacter pylori, and pregnancy; men 8 to 10 times more likely to develop CSC than women; study — in series of women, mean age of onset 47 yr; 62% achieved complete anatomic recovery in median of 5 mo; outcomes more favorable in patients with disease of shorter duration, single occurrence, subretinal precipitates (suggesting recent onset), absence of pigment epithelial detachment, lack of hormone replacement therapy, and young age; drugs associated with CSC include pseudoephedrine, ecstasy, possibly other sympathomimetics, sildenafil (Viagra), and steroids

Clinical examination: FA — smokestack rare sign seen in early CSC; pigment mottling with window defect seen in chronic stage; multiple pinpoint leakages seen in chronic or steroid-associated CSC;
in advanced cases, areas of atrophy with window defect present; ICG can distinguish CSC from PCV; in early stages, autofluorescence studies show darkening and pinpoint hyperfluorescence; in chronic CSC, widespread mottling common; gravity-induced picture on UWFA pathognomonic for CSC; OCT — in early stages, no intraretinal fluid seen and photoreceptors elongated; in chronic disease, photoreceptors atrophy; in late stages, intraretinal fluid possible; choroidal thickness increased in patients with CSC, Vogt-Koyanagi-Harada syndrome, or PCV

Management: Best treatment unknown; medication history should be assessed; conventional thermotherapy or micropulse laser therapy (MLT) reasonable if leak far from fovea; MLT given in acute CSC; complications may be reduced by reducing dose of verteporfin, laser energy, or laser time in half; use of full fluence for extrafoveal lesions and half fluence for foveal lesions associated with anatomic success and improvements in vision, even in patients with steroid-induced chronic CSC

Experimental options: intravitreal bevacizumab — rationale for use lacking because no NV present; levels of VEGF and IL-8 not increased in CSC; glucocorticoid antagonists — include ketoconazole, RU-486 (mifepristone), and rifampin; rifampin may increase endogenous production of steroids; methotrexate also studied; antimetalloproteinase agents — if spironolactone (Alduc- tone) used, level of potassium should be monitored

Suggested Reading

1. Which of the following is the earliest sign of age-related macular degeneration (AMD)?
   (A) Drusen  (C) Thickening of Bruch membrane
   (B) Choroidal neovascularization  (D) Atrophy of retinal pigment epithelium

2. A patient with one large drusen measuring 150 μ and 4 drusen measuring 70 to 100 μ has ________-stage AMD.
   (A) Early (B) Intermediate  (C) Advanced

3. Which of the following is the strongest risk factor for AMD?
   (A) Smoking  (B) Advanced age  (C) Hypertension (D) Family history

4. The original Age-related Eye Disease Study (AREDS) formula contains:
   1. Vitamin C
   2. Vitamin E
   3. Zinc
   4. Lutein
   5. Zeaxanthin
   6. ω-3 fatty acids
   7. β-carotene
   8. Copper
   (A) 1,2,3,4,5  (B) 1,2,3,7,8  (C) 1,2,3,4,7  (D) 3,4,5,6,7,8

5. Choose the true statement about photodynamic therapy for the treatment of AMD.
   (A) Repeated monthly  (C) Most effective for occult neovascularization
   (B) Causes minimal damage to surrounding tissues  (D) Improves visual acuity

6. Which of the following agents specifically blocks the 165 isoform of vascular endothelial growth factor (VEGF)?
   (A) Ranibizumab  (B) Bevacizumab (C) Aflibercept (D) Pegaptanib

7. The Comparison of AMD Treatments Trials (CATT) and the Inhibition of VEGF in Age-related CNV (IV AN) trial both showed that treatment with ranibizumab was ________ to treatment with bevacizumab and that an as-needed treatment schedule was ________ to monthly treatment.
   (A) Superior; inferior  (C) Superior; superior
   (B) Equivalent; equivalent  (D) Equivalent; inferior

8. The VIEW 1 and VIEW 2 studies suggested that aflibercept may be preferable to ranibizumab for treatment of AMD because aflibercept:
   (A) Is approved by the Food and Drug Administration
   (B) Provides a longer duration of effect  (C) Is more efficacious
   (D) Provides a broader spectrum of inhibition of VEGF

9. The main conclusion of the REVOLUTION study was that patients with retinal vein occlusion who are treated with scatter laser plus ranibizumab:
   (A) Have an excessive rate of adverse events  (B) Have better visual acuity outcomes than patients treated with ranibizumab alone
   (C) Require fewer injections of ranibizumab than patients treated with ranibizumab alone  (D) Derive no benefit unless they have early disease

10. Which of the following signs suggests an early stage of disease in a patient with central serous chorioretinopathy?
    (A) Smokestack sign on fluorescence angiography (FA)  (B) Widespread mottling on FA
    (C) Intraretinal fluid on optical coherence tomography (OCT)  (D) Atrophy of photoreceptors on OCT