The Latest on AMD
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Course Description
This update will cover recent advances in technology and therapeutics that are improving our understanding and ability to diagnosed and treat age-related macular degeneration (AMD) early.

Goal
Provide attendees with the latest information on AMD and discuss integration of innovative diagnostic modalities into clinical practice to aid early diagnosis.

Learning Objectives
At the conclusion of this course, attendees will be able to:

1) Understand the latest on AMD (i.e. prevalence, risk factors, classifications)
2) Appreciate advance technologies and methodologies to analyze AMD including fundus autofluorescence (FAF), wide-field imaging, multi-modal imaging with SD-OCT and OCT angiography (OCTA), and fluorescein angiography.
3) Incorporate into practice recent study results in the management of AMD
4) Enhance patient care by evaluating the current array of treatment options and clinical trial opportunities

Abstract:
Age-related macular degeneration is a leading cause of blindness in people 65 or older. Therefore, early diagnosis, intervention, and treatment are essential to improve visual outcome. This course will cover the latest information on AMD.
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COURSE OUTLINE

I. Prevalence of AMD
- Age-related macular degeneration (AMD) is a leading cause of severe, irreversible vision impairment in developed countries.
- In 2004, it was estimated that approximately 1.75 million people aged 40 years or older in the United States were estimated to have either neovascular AMD or geographic atrophy in at least one eye, and 7.3 million were considered to have high-risk features, such as large drusen ($\geq 125 \mu m$) in one or both eyes.
- Earlier estimates suggested that the 1.75 million individuals affected by advanced AMD in at least one eye are expected to increase to nearly 3 million.
- The prevalence of AMD varies by ethnicity.
  - In the Beaver Dam Eye Study (Caucasian population), the prevalence of any AMD was less than 10% in persons aged 43 to 54 years yet more than tripled for persons aged 75 to 85 years of age.
- Progression to any AMD over a 10-year period was 4.2% for persons aged 43 to 54 years and 46% for those aged 75 years and older by year 2020.
- Risk factors for progression
  - Modifiable – Smoking, chronic sunlight or blue light exposure, low MPOD, obesity (BMI), hypertension, hypercholesterolemia, and poor nutrition
  - Non-modifiable - Age, gender, GENETICS, family history, and Caucasian

II. Classification of AMD
- There are different classifications of AMD in the literature.
- The AREDS was a prospective multicenter randomized clinical trial conducted between 1992 and 2006 designed to assess the natural course and risk factors for age-related cataract and AMD. We will review the classification used by the Age-Related Eye Disease Study (AREDS) since current treatment recommendations are based on this classification.
- Review of AREDS 1 and 2
  - AREDS 1 Results
    - 20% risk reduction in vision loss for patients with intermediate AMD
    - 25% risk reduction to advanced AMD for patients with intermediate AMD
  - AREDS 2 -18% reduction in progression in subjects who received L&Z + AREDS 1 supplement (without beta carotene) compared to those who took the original AREDS 1 supplement with beta carotene
  - Classification of AMD from the AREDS
No AMD - 0 - 5 small drusen (<63 µm in diameter)
Early AMD - multiple small drusen, few intermediate drusen (63–124 µm in diameter), or mild RPE abnormalities.
Intermediate AMD - Numerous intermediate drusen, at least one large druse (125 µm or larger in diameter), Geographic atrophy (GA) not involving fovea
Advanced AMD
  o GA - involving the foveal center
  o Choroidal neovascularization (CNV)

III. Anatomy and Physiopathology of the macula
- The macula is an oval- shaped pigmented area in the center of the retina.
  o The human macula has a diameter of around 5.5 mm (0.22 in) and is subdivided into the umbo, foveola, foveal avascular zone, fovea, parafovea, and perifovea areas. The anatomical macula at 5.5 mm (0.22 in) is much larger than the clinical macula which, at 1.5 mm (0.059 in), corresponds to the anatomical fovea. The anatomical macula is defined histologically in terms of having two or more layers of ganglion cells. The umbo is the center of the foveola which in turn is located at the center of the fovea. The fovea contains the largest concentration of cone cells.
  o The retina contains two types of specialized nerve cells (photosensitive cells), the rods and the cones. Cellular structure and function of rods and cones will be reviewed with emphasis of their role in AMD development.
  o The macula is yellow in color and it absorbs excess blue and ultraviolet light that enter the eye, acting as a natural sunblock.
  o The macula is responsible for the central, high- resolution, color vision that is possible in good light; and this kind of vision is impaired if the macula is damaged in macular degeneration
  o The yellow color comes from its content of lutein and zeaxanthin, which are yellow xanthophyll carotenoids, derived from the diet. Zeaxanthin predominates at the macula, while lutein predominates elsewhere in the retina.
  o There is some evidence that these carotenoids protect the pigmented region from oxidative damage. Clinical relevance, evaluation and supplementation with oral carotenoids in AMD patients will be reviewed.

IV. Imaging Techniques
- OCT is important in early detection and follow up of non- exudative or “dry” AMD. Optical coherence tomography defines the cross- sectional architecture of the retina that is not possible with any other imaging technology. OCT has greatly enhanced our understanding of macular anatomy.
  o Multiple examples of imaging of drusen, non- vascularized PEDS, and geographic atrophy with clinical correlations will be provided.
  o OCT also helps monitoring natural progression of AMD and evaluating the response of the retina and RPE to therapy by allowing structural changes to be followed accurately.
  o Newer generation OCT including SD OCT and OCTA have increased the image
resolution and enhanced our ability to detect structural changes of the retina and choroid.

- Next-generation technology, including swept-source OCT, is evolving at this time and is not currently approved by the FDA. Enhanced depth imaging improves our ability to assess the structure of the choroid. Clinical examples of these new applications will be provided.
- Fundus autofluorescence (FAF) is a relatively new imaging technique that can be used to study retinal diseases such as dry AMD. Lipofuscin (LF) and melanolipofuscin are the main sources of retinal AF.
  - These fluorophores are endogenous, thereafter there is no need to inject any dye to acquire FAF images. Because of age-related or pathologic accumulation/depletion of fluorophores within the retinal pigment epithelium (RPE) cells and retinal tissue, FAF can show changes in the integrity and metabolism of retinal cells.
  - Several different pathologies can be detected. Peculiar AF alterations can help the clinician to monitor disease progression and to better understand its pathogenesis. We will review FAF principles and clinical applications.

- **Home Testing**
  - ForeSee Home monitoring

V. Treatment of Non-exudative AMD

- AMD and Vitamin Supplementation. Review of the Results of the AREDS Study
- Geographic atrophy (GA) is a debilitating form of AMD that leads to irreversible vision loss, with no available treatment. GA secondary to AMD is a significant unmet medical need, with no approved or effective treatments. Loss of vision in patients with GA is caused by progressive atrophy of the retina. There is currently no effective treatment to prevent either onset or progression of GA.
  - Initial attempts for pharmacologic treatment if this condition have been studied in recent clinical trials. Lampalizumab is a complement-targeting compound that showed efficacy in a Phase II study in patients with GA. Phase II MAHALO Study results will be presented.
  - Brimonidine, a selective alpha-2 adrenergic agonist, has a long history of clinical use for treatment of open-angle glaucoma and ocular hypertension. In vitro and in vivo data provide evidence that brimonidine has cyto/neuroprotective effects, suggesting potential utility for the treatment of GA secondary to AMD.
  - We will review rationale and background information of the upcoming Phase 3 trial to determine the Efficacy and Safety of Brimonidine Drug Delivery System (Brimo DDS®) in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration
• **Differential diagnosis of Dry AMD**
  o Not all atrophic and pigmentary macular changes correspond to dry macular degeneration.
  o Clinical examples of macular conditions that may be differentiated from Non-Exudative Age- related macular degeneration will be provided and discussed emphasizing the features and characteristics that facilitate a differential diagnosis.
    o These will include macular dystrophies, dominant Drusen, Malattia Leventinese, Myopic maculopathy, Chloroquine and Tamoxifen maculopathy, macular scars, solar maculopathy, OHS, cicatricial ICSCR and non- exudative juxta foveal *Wet ARMD*

**VI. Wet ARMD Treatment**

• **Past Treatment**
  o Macular Photocoagulation
  o Visudyne Photodynamic therapy

• **Current Treatments**
  o History of VEGF
  o Anti VEGF Medications
    Avastin
  o Lucentis
  o Anchor and Marina Lucentis Studies Eylea
  o View Study Standard Care Results

• **Wet ARMD Treatment coming soon**

• **Brolucizumab**
  o Hawk and Harrier Study Results

• **Clinical Research in Wet ARMD**
  o Darpin / Abicipar
  o Cedar and Sequoia Study
  o Faricimab
  o Tenaya and Lucerne Study Port Delivery System
  o Archway trial