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Imaging Protocols in Clinical Studies in Advanced Age-Related Macular Degeneration

Recommendations from Classification of Atrophy Consensus Meetings

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Purpose: To summarize the results of 2 consensus meetings (Classification of Atrophy Meeting [CAM]) on conventional and advanced imaging modalities used to detect and quantify atrophy due to late-stage non-neovascular and neovascular age-related macular degeneration (AMD) and to provide recommendations on the use of these modalities in natural history studies and interventional clinical trials.

Design: Systematic debate on the relevance of distinct imaging modalities held in 2 consensus meetings.

Participants: A panel of retina specialists.

Methods: During the CAM, a consortium of international experts evaluated the advantages and disadvantages of various imaging modalities on the basis of the collective analysis of a large series of clinical cases. A systematic discussion on the role of each modality in future studies in non-neovascular and neovascular AMD was held.

Main Outcome Measures: Advantages and disadvantages of current retinal imaging technologies and recommendations for their use in advanced AMD trials.

Results: Imaging protocols to detect, quantify, and monitor progression of atrophy should include color fundus photography (CFP), confocal fundus autofluorescence (FAF), confocal near-infrared reflectance (NIR), and high-resolution optical coherence tomography volume scans. These images should be acquired at regular intervals throughout the study. In studies of non-neovascular AMD (without evident signs of active or regressed neovascularization [NV] at baseline), CFP may be sufficient at baseline and end-of-study visit. Fluorescein angiography (FA) may become necessary to evaluate for NV at any visit during the study. Indocyanine-green angiography (ICG-A) may be considered at baseline under certain conditions. For studies in patients with neovascular AMD, increased need for visualization of the vasculature must be taken into account. Accordingly, these studies should include FA (recommended at baseline and selected follow-up visits) and ICG-A under certain conditions.

Conclusions: A multimodal imaging approach is recommended in clinical studies for the optimal detection and measurement of atrophy and its associated features. Specific validation studies will be necessary to determine the best combination of imaging modalities, and these recommendations will need to be updated as new imaging technologies become available in the future. *Ophthalmology 2016;■:1–15 © 2016 by the American Academy of Ophthalmology*

*Supplemental material is available at www.aaojournal.org.

In industrialized countries, late-stage age-related macular degeneration (AMD) is the leading cause of legal blindness in the elderly.[1,2] It presents with neovascularization (NV) or geographic atrophy (GA).[3] Both manifestations are not mutually exclusive; atrophy develops in eyes with NV effectively treated with intravitreal anti-vascular endothelial growth factor (VEGF) injections both within and outside the area of NV.[4–7] In eyes developing atrophy without

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initial signs of NV, GA may be complicated by NV over time. The term "GA" has been used with various definitions in the past as recently reviewed.[8] In the current article, we use the term "GA" for complete retinal pigment epithelium (RPE) and outer retinal atrophy, excluding any region of presumptive NV. In this sense, GA can be present in eyes with no evident signs of active or regressed NV (non-neovascular AMD) and in eyes with active or regressed NV outside the NV region (neovascular AMD).

The use of intravitreal VEGF inhibitors has led to an unprecedented improvement in functional outcomes for patients with neovascular AMD, significantly reducing the incidence of blindness in the elderly.[9] However, visual outcomes of neovascular AMD treated with intravitreal anti-VEGF therapy often are limited by the occurrence of atrophy or fibrosis.[10] Many potential pathogenic factors are thought to cause the formation of atrophy in eyes with AMD, and some pathways are being targeted with pharmacologic agents in clinical development.[11] No approved drugs are currently available to significantly slow atrophy progression and its associated vision loss.

Recent advances in retinal imaging technology, including spectral-domain optical coherence tomography (SD OCT) and swept-source optical coherence tomography (SS-OCT), scanning laser ophthalmoscopy (SLO) modalities, and widefield imaging, have markedly improved the detection of atrophy and the morphologic biomarkers associated with disease progression. Anatomic end points have been validated recently and introduced as primary outcome parameters in interventional clinical trials for atrophic AMD with acceptance by regulatory authorities.[12–15] Scanning laser ophthalmoscopy–based fundus autofluorescence (FAF) imaging together with semiautomated analysis tools and en face OCT imaging are most commonly used for the delineation and quantitation of GA areas.[14,16–18] Correlating the functional consequences of atrophy is highly relevant to clinical trials and clinical care of the condition. At this time, spatial resolution of these imaging modalities is far superior to currently available functional tests, such as fundus-controlled perimetry (including so-called microperimetry with tracking of eye movements).

Selection of appropriate imaging modalities is a key factor for studies evaluating the efficacy of drugs in eyes with advanced AMD. Optimized selection of these modalities may be critical to detect an efficacy signal, and the choice may affect the duration and cost of such studies. A major challenge is the fast pace of technologic development in imaging devices and image analysis algorithms with a concurrent lack of timely validation. Each modality has its strengths and weaknesses. Moreover, the use of a single imaging modality may not be optimal, and multimodal imaging may be a sensible approach to obtain the most reliable detection and measurement of atrophy.[19]

The Classification of Atrophy Meeting (CAM) was organized to gather an international group of experts (Appendix 1, available at www.aaojournal.org), including representatives of established reading centers, to evaluate currently available imaging technologies and to propose consensus recommendations regarding the modalities to be used in interventional trials and in natural history studies of both non-neovascular and neovascular AMD, particularly taking into account the need for detection, quantification, and monitoring of atrophy over time. We present the results of these consensus meetings.

Methods

The planning committee for the CAM consisted of 3 retinal experts who developed the format for the consensus proceedings. The composition of the consensus panel was determined on the basis of previous notable scientific contributions to the field. Participants are listed in Appendix 1 (available at www.aaojournal.org). During 2 consensus meetings (CAM-1 and CAM-2 held in 2015), these experts discussed and evaluated the advantages and disadvantages of various imaging modalities proposing the optimal combination for use in future natural history and interventional clinical studies. The formats of both meetings included the collection and discussion of clinical cases by the participants. A pre-meeting exercise also was distributed in preparation of the meetings aiming to identify strengths and challenges for detection of atrophy in each imaging modality. Furthermore, a list of imaging modalities currently used in large-scale clinical trials in AMD was prepared for future discussion. During a first session of CAM-2, cases and study questions were discussed to provide a common basis for the consensus finding process. Next, a debate was held on each of the listed imaging modalities. Within the debate, it was questioned which particular advantages and disadvantages existed for each modality and which acquisition systems and protocols were best used. Furthermore, there was systematic discussion of the role each modality should play in future studies in non-neovascular and neovascular AMD. Finally, a grading system was used to classify each modality as (1) R = recommended, (2) O = optional, (3) N = not recommended, or (4) D = at the discretion of the sponsor. If no consensus was achieved during the debate, then a decision was obtained by majority vote. Results of the debate were logged.

Results

Color Fundus Photography

Color fundus photography (CFP) has been the historical standard used for documenting funduscopic abnormalities, and it is still used in current AMD trials.[12,20,21] Color fundus photography was the basis of studies performed before the advent of many newer forms of imaging. Therefore, the continued use of CFP in future studies is necessary to ensure comparability with data gathered from the newer modalities and to allow comparison with past studies. In addition, CFP with its broad spectrum of illumination is the closest imaging modality to correlate with clinical ophthalmoscopy. With CFP, it is possible to detect a wide array of phenotypic alterations associated with AMD, including drusen, crystalline deposits, pigmentary changes, lipid, atrophy, and fibrosis, as well as neovascular findings such as hemorrhages, fluid, and exudate (Figs 1A and 2A). Yet, compared with other imaging modalities, it has relatively low contrast, which makes identification and quantification of atrophic lesions and other AMD-associated changes challenging. For instance, without previous processing, CFP provided a sensitivity of only 33% to 42% for the detection of reticular pseudodrusen, an important risk factor for fast GA progression (Fig 1A–D).[22,23] Moreover, the use of high-intensity and broad-spectrum light makes CFP