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Anatomic Clinical Trial Endpoints for Nonexudative Age-Related Macular Degeneration

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Topic: To review the role of anatomic endpoints in clinical trials for the study of nonexudative age-related macular degeneration (AMD) with an emphasis on a novel composite endpoint for the study of emerging therapies for intermediate AMD (iAMD).

Clinical Relevance: Unlike clinical trials for exudative AMD, it is impractical to use the change in visual acuity (VA) as a primary endpoint for the study of nonexudative AMD. By the time VA has been lost in nonexudative AMD, proof-of-concept early-stage clinical trials would take years to run, and drug development would be a near impossible task. Surrogate endpoints are needed that reliably predict future vision loss and can be easily measured. Anatomic changes that correlate with disease progression in nonexudative AMD offer the greatest promise as primary endpoints.

Methods: In preparation for this review, the electronic PubMed database was searched for relevant research pertaining to anatomic endpoints for the study of nonexudative AMD. Paper selection was based on our knowledge of the field with the goal to be as inclusive as possible. Whenever possible, recent review articles and results from large clinical trials, preferably with outcomes from many years of follow-up were favored over trials of short duration.

Results: The most commonly used anatomic endpoint for the study of late, nonexudative AMD is the growth of geographic atrophy (GA). The advantages of studying GA include the appreciation that its enlargement through the foveal center leads to significant vision loss through the availability of natural history studies, the understanding that prevention of this growth would preserve vision in the future, the ability to reliably measure GA using different imaging strategies, and the development appropriate statistical tools that reliably predict the growth of GA over time. The major disadvantage of using GA is that significant, irreversible disease progression has already occurred. The use of drusen volume as a predictor of disease progression and the use of a composite endpoint that incorporates drusen growth, formation of GA, and formation of neovascularization offers an opportunity to study therapies at an earlier stage of AMD with a greater likelihood of preserving better vision over a lifetime.

Conclusions: Anatomic endpoints for the study of nonexudative AMD are needed to accelerate drug development, and the availability of optical coherence tomography algorithms capable of reliably measuring drusen morphology offer the best opportunity to study therapies for iAMD. *Ophthalmology 2016;■:1–20 © 2016 by the American Academy of Ophthalmology.*

Age-related macular degeneration (AMD) is a common, late-onset, slowly progressive, complex disorder responsible for irreversible blindness among the elderly worldwide.[1–3] The signs, symptoms, and clinical progression of AMD have been well described, and the most recent classification system separates AMD into 3 distinct stages: early, intermediate, and late.[4] The hallmarks of early AMD include medium-sized drusen ($\geq$63 and $<$125 μm) without pigmentary abnormalities. The features of intermediate AMD (iAMD) include large drusen ($\geq$125 μm) with or without pigmentary abnormalities or medium-sized drusen with pigmentary abnormalities. Late AMD is characterized by the presence of macular neovascularization (MNV) and/or geographic atrophy (GA) (Fig 1). In general, the term "nonexudative AMD" refers to all stages of early, intermediate, and late AMD that do not involve any neovascularization or exudation. When neovascularization arises in the setting of nonexudative AMD, the disease is then referred to as exudative AMD, but the underlying nonexudative AMD is still present and may progress unabated. Although neovascularization occurs in only 15% to 20% of patients with AMD, it has been the focus of most therapeutic interventions because of the rapid, sustained, and irreversible severe vision loss associated with neovascularization if left untreated. In contrast to exudative AMD, the vision loss associated with nonexudative AMD is more of a gradual process, taking years to progress.[5] With the successful development of drugs that inhibit vascular endothelial growth factor (VEGF), the rapid, severe vision loss from exudative AMD can be prevented. However, even with successful anti-VEGF therapy, patients continue to

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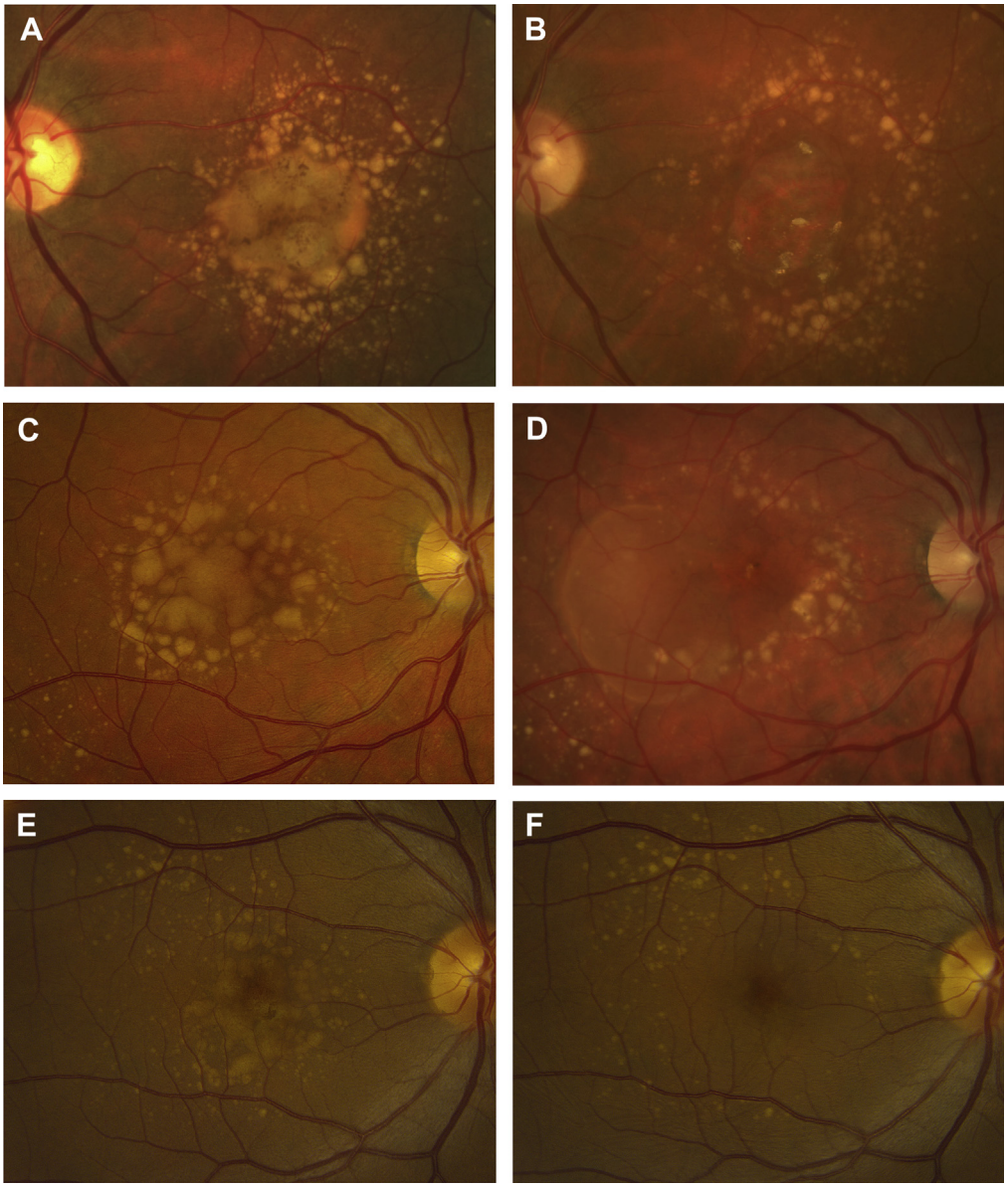

Figure 1. Color fundus images of 3 patients with intermediate age-related macular degeneration (AMD) showing disease progression and 3 different outcomes over time. **A**, **B**, Progression to geographic atrophy (GA) in the left eye of a 60-year-old man with large confluent drusen and pigmentary abnormalities in the central macula. After 3 years, drusen regression led to GA. **C**, **D**, Progression to macular neovascularization (MNV) in the right eye of a 74-year-old woman with large confluent drusen in the central macula. The drusen partially resolved, and the patient developed MNV in an area temporal to the fovea 4 years after first presentation. **E**, **F**, Drusen resolution without progression to late AMD in the right eye of a 61-year-old woman with large confluent drusen and pigmentary abnormalities in the central macula. Within 1 year after presentation, the drusen resolved without formation of MNV or GA (**F**).

slowly lose vision from the nonexudative disease, and macular atrophy often results after prolonged anti-VEGF therapy.[6–9] This macular atrophy can have an appearance similar to GA, and whether anti-VEGF therapy accelerates the formation or growth of GA remains controversial.

One strategy to improve long-term visual acuity outcomes when treating exudative AMD is to target additional pathways involved in the neovascular process. Another strategy, and perhaps an even better one, would be to stop or slow the underlying nonexudative AMD at an earlier stage when more visual acuity could be preserved. Promising therapies for nonexudative AMD are now being investigated, but to do so, it is necessary to design reliable clinical trials to test these novel therapies. Although the long-term goal of any treatment is to preserve vision, it is unrealistic to use visual acuity as a clinical trial endpoint in nonexudative AMD because vision loss takes many years to develop. This is a particular problem for early stage, proof-of-concept clinical trials in which it is impractical to use visual acuity as an endpoint and wait years to determine whether a treatment even seems to be effective so that longer, later-phase trials can be performed. For this reason,