

Imaging and Pharmacologic Approaches in the Treatment of Geographic Atrophy in AMD

Imaging with FAF offers new insight into how and why GA progresses in some patients.

BY FRANK G. HOLZ, MD

In the past decade, great strides have been made in the treatment and management of exudative age-related macular degeneration (AMD). The treatment of “dry” or nonexudative AMD, however, remains an unmet clinical need. Advanced atrophic dry AMD, or geographic atrophy (GA), is a frequent cause of visual loss with a high incidence, especially in the elderly. The Beaver Dam Eye Study found that, in individuals aged greater than 85 years, the incidence of GA was 8%, compared with an incidence of 2% for neovascular AMD.¹

It is also recognized that development of atrophy still contributes to visual loss in the late stages of exudative AMD, despite successful antiangiogenic treatment with vascular endothelial growth factor inhibitors. An efficacious therapy for atrophic AMD, therefore, could be of benefit in both the wet and dry forms of the disease.

FUNDUS AUTOFLUORESCENCE IMAGING

Fundus autofluorescence (FAF) imaging is a recently developed imaging method for topographic mapping of lipofuscin distribution in the retinal pigment epithelium (RPE). Accumulation of lipofuscin—a mixture of various molecular species including toxic molecules—in the lysosomal compartments of RPE cells is a common downstream pathogenetic pathway in a number of hereditary and complex retinal diseases, including AMD.^{2,3}

Longitudinal observation with FAF in the Fundus

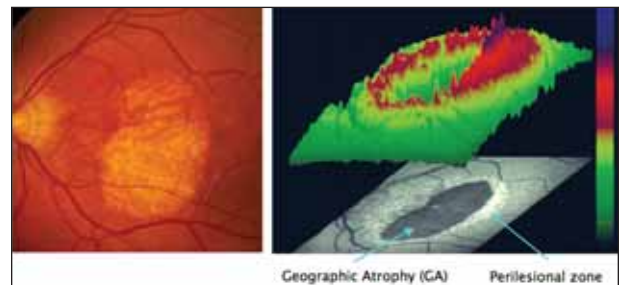


Figure 1. Fundus autofluorescence (FAF) imaging can provide topographic mapping of lipofuscin distribution in the retinal pigment epithelium.

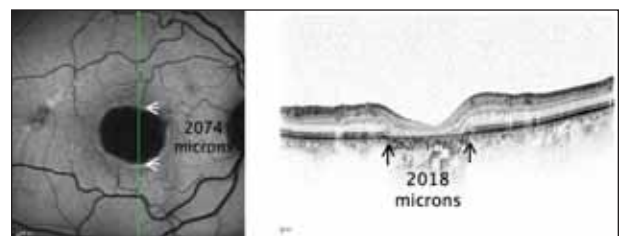


Figure 2. “Atrophy” in FAF images corresponds with photoreceptor drop-out.

Autofluorescence in Age-related Macular Degeneration (FAM) Study^{4,5} showed that areas with increased FAF signals may precede the enlargement of GA and the development of new areas of atrophy.

Figures 1 and 2, taken with the Spectralis HRA+OCT

(Heidelberg Engineering, Heidelberg, Germany), show the correspondences among lipofuscin distribution in the RPE, "atrophy" in FAF images, and photoreceptor drop-out. While the atrophic central patch in Figure 1 shows a markedly increased FAF signal due to absent RPE, there is an increased signal in the perilesional zone representing incipient atrophy.

The size of atrophic patches represents a meaningful anatomic endpoint for interventional studies in patients with GA. These areas are easily identified and quantified using automated image analysis software in conjunction with FAF obtained with a confocal scanning laser ophthalmoscope. The identification of high-risk features based on perilesional FAF patterns in patients with advanced dry AMD⁵ may allow investigators to enrich patient populations for fast progressors so as to minimize the sample sizes needed, to better demonstrate possible treatment effects, and to reduce the observational period needed to show treatment effects in this overall slowly progressive disease.

Experimental evidence suggests that accumulation of lipofuscin and its molecular component A2-E (N-retinylidene-N-retinylethanolamine) in the RPE are implicated in a number of toxic effects, including inhibition of lysosomal function, destabilization of membranes through a detergent effect, and activation of complement.⁶⁻⁸

There is an absence of evidence linking other potential risk factors, including smoking, hypertension, diabetes, or body mass index, with progression of GA. The genetic risk alleles that have been associated with AMD have shown no association with progression of GA.⁹

Taken together, these findings suggest a rationale to reduce the accumulation of lipofuscin and A2-E, which are byproducts of the visual cycle, to slow or prevent the progression of GA in dry AMD. A number of pharmaceutical agents are currently under evaluation that also tackle other pathways, including neuroprotection and complement inhibition. A complete list would be beyond the scope of this article. Some notable ongoing trials are described below.

FENRETINIDE

Fenretinide (Sirion Therapeutics) is an orally administered synthetic retinoid derivative that competes with retinol for binding to the retinol-binding protein. Its proposed role in the treatment of GA is to inhibit vitamin A delivery to the eye by reducing systemic levels of retinol, a precursor of A2-E. Preclinical work has shown that fenretinide prevents the accumulation of retinol in the RPE. A prospective, randomized clinical trial assessing the safety and efficacy of fenretinide in patients with GA in one or both eyes is ongoing.¹⁰

ACU-4429

Acucela's ACU-4429 is an orally administered non-retinoid small molecule visual cycle modulator. In a phase

1 single-center dose-ranging study, electroretinography demonstrated that ACU-4429 successfully modulated the visual cycle, according to Acucela.¹¹

Toxic byproducts of the visual cycle, formed from all-trans-retinal, are often associated with lipofuscin deposits in the RPE. Preclinical studies¹² showed that excessive production of toxic byproducts of the visual cycle can lead to retinal degeneration in mice. In mice lacking a gene encoding a protein critical for clearing all-trans-retinal from photoreceptors, the severity of visual dysfunction was attenuated by treatment with retinylamine. Mice lacking this gene, when treated with ACU-4429 daily for 3 months, showed a reduction in A2-E fluorescence in the RPE. (Data courtesy Acucela.)

OT-551

Othera Pharmaceuticals' OT-551 is a topical antioxidant and antiinflammatory small molecule. The compound protected photoreceptor cells from light-induced damage in animal studies.¹³ In a phase 2 clinical trial, OT-551 showed a trend toward reducing moderate vision loss (15 letters or more) in patients with GA compared with placebo.¹⁴ The trend was more pronounced in subgroups based on GA characteristics or level of visual acuity at baseline.

CNTF

Ciliary neurotrophic factor (CNTF) is a growth factor that has been shown to increase the thickness of the retina and the outer nuclear layer of photoreceptors in animal models. Neurotech has developed an encapsulated cell technology in which human cells are genetically modified to secrete CNTF. An encapsulated cell implant in the vitreous cavity continuously releases a therapeutic dose. In a phase 2 multicenter clinical trial, NT-501 achieved safe intraocular delivery of CNTF for 1 year. A potential for a therapeutic effect was seen in eyes with GA, in both retinal thickness change and visual function.¹⁵

POT-4

Potentia has developed a synthetic peptide to bind to complement component C3, preventing its participation in the complement activation cascade. Intravitreal application has been shown to be safe in a phase 1 clinical trial.¹⁶

AL-8309B

Recruitment has been completed for a double-masked, randomized, phase 3 clinical study to evaluate the effects of topically administered AL-8309B (Alcon Laboratories) on the progression of geographic atrophy (GATE Study). The mean outcome parameter is the mean annualized atrophic lesion growth quantified in confocal SLO/FAF images.¹⁷

CONCLUSIONS

Late stage dry AMD is increasing in prevalence with the aging of the population, and GA is a frequent cause of severe visual loss. With the recent therapeutic advances in neovascular AMD, building a therapeutic arsenal against the dry form is the next major challenge in addressing this sight-threatening disease. Understanding of its pathogenesis is still incomplete, however. Continued multidisciplinary research is needed to improve our insights into the disease and identify novel targets for treatment.

A number of promising therapeutic targets have been identified, and clinical trials have been initiated. Their results will guide us in designing further trials and finding additional treatment targets, with the hope of preventing severe vision loss from this age-related disease. ■

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