Supplement to November/December 2020

Release Date: November 2020
Expiration Date: December 2021

RT Retina Today

EPIDEMIOLOGY OF DRY AMD AND GA

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a webinar plus a live question-and-answer session.

ACTIVITY DESCRIPTION

Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD) for which there is currently no treatment approved by the US FDA. This supplement summarizes the latest information on GA, including the investigative therapies showing positive outcomes in clinical trials and insight from the expert faculty who share their expertise related to the optimal imaging modalities for evaluating GA and case studies.

TARGET AUDIENCE

This certified CME activity is designed for retina specialists who care for patients with dry AMD and GA.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- Describe the prevalence of AMD and classify by severity: early, intermediate, and advanced (ie, wet AMD and GA)
- Explain the pathogenesis of GA
- Distinguish which imaging modalities are best suited for GA evaluation
- Categorize new therapies in the pipeline for GA
- Evaluate the functional and anatomic outcomes used in managing patients with GA

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PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation/ Satisfaction Measures Form for CME Credit.

1. Please rate your confidence in your ability to distinguish which imaging modalities are best suited for geographic atrophy (GA) evaluation (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. According to the Age-Related Eye Disease Study (AREDS), what percentage of patients in the highest risk category for macular degeneration progressed to central GA?

a. 24.6%
b. 30.8%
c. 42.7%
d. 53.9%

3. Which of the following statements about GA is NOT true:

a. GA accounts for ~35% of all advanced age-related macular degeneration (AMD) cases
b. GA accounts for 20% of all legal blindness attributed to AMD
c. Prevalence of GA increases with age
d. The AREDS study showed a higher risk of progression to neovascular AMD than GA in patients with high-risk macular degeneration

4. Which of the following is the description of Intermediate AMD (Category 3) according to the AREDS study?

a. Presence of GA involving the fovea and/or features of neovascular AMD
b. Multiple small drusen, few intermediate drusen, RPE abnormalities
c. Extensive intermediate drusen, and at least one large drusen; GA not involving the center of the fovea
d. None or few small drusen

5. All of the following are risk factors that lead to advanced AMD and GA EXCEPT:

a. Aging
b. Family History
c. Smoking
d. Genetic predisposition and diet
e. High intraocular pressure

6. Which of the following statements about risk factors for AMD is true?

a. Females are at higher risk of developing AMD than males
b. Males are at higher risk of developing AMD than females
c. Smoking is not a significant risk factor for AMD
d. Increasing age is not a significant risk factor for AMD

7. Which of the following is NOT a function of the retinal pigment epithelium?

a. Brings nutrients to the photoreceptor layer
b. Recycles photoreception waste through phagocytosis of photoreceptor outer segments
c. Maintains the integrity of the outer blood-retinal barrier through tight junctions
d. Maintains a dense network of blood vessels to supply oxygen and nutrients to the outer retina

8. Which of the following imaging modalities can visualize the distribution of lipofuscin to allow mapping of the size of GA?

a. Fundus color photography
b. Fundus autofluorescence
c. Optical coherence tomography
d. B-scan ultrasonography

9. Which pattern of hyperautofluorescence on fundus autofluorescence imaging is linked with strong evidence of higher rate of GA progression?

a. None
b. Focal
c. Diffuse trickling

10. You are seeing Ms. Smith for a routine eye exam. She is a 65-year-old white woman who has recently noticed difficulty focusing. On exam, you note one drusen, approximately 140 microns in diameter, along with retinal pigment epithelium abnormalities. Which of the following is the best statement to counsel this patient?

a. You have mild early changes consistent with early macular degeneration. I do not recommend any treatment.
b. You have mild early changes consistent with early macular degeneration. I recommend you start using an Amsler Grid.
c. You have changes consistent with intermediate macular degeneration. I do not recommend any treatment.
d. You have changes consistent with intermediate macular degeneration. I recommend you start AREDS2 supplementation, avoid smoking, use sun protection, and monitor for further changes using an Amsler Grid.

Epidemiology of Dry AMD and GA

EPIDEMIOLOGY OF DRY AMD AND GA

A review of data, demographics, and risk factors.

BY RISHI P. SINGH, MD

Age-related macular degeneration (AMD) is the leading cause of blindness among white Americans,[1] and is the second-leading cause of blindness among American Hispanics.[2] Classification of early, intermediate, and advanced stages of AMD is well understood, and disease in the advanced state is classified as either central geographic atrophy (GA) or neovascular AMD.[3,4] Anti-VEGF agents are effective at treating patients with neovascular AMD, and there are no approved therapies for intermediate dry AMD or GA.

The dearth of treatment options for GA is particularly concerning when one notes that the Age-Related Eye Disease Study (AREDS) group found that a majority of patients (53.9%) who progressed to advanced AMD during a 10-year study period demonstrated central GA.[5] Approximately 80 to 95% of patients with AMD develop some atrophic form of the disease, and approximately 30% of them progress to GA.[6,7]

Clinically, GA is defined by the presence of irreversible central scotoma, which present as areas of depigmentation of the retinal pigment epithelium (RPE) with sharp-bordered margins (Figure 1). Classification schemes, which are discussed in this article, guide categorizing disease severity.

GROWING NEED

An estimated 2 million patients had AMD in 2010 in the United States. That number is expected to grow to 3.6 million and 5.4 million in 2030 and 2050, respectively.[8] Globally, 196 million patients and 288 million patients are expected to have any form of AMD in 2020 and 2040, respectively.[7] GA accounts for approximately 35% of advanced AMD cases, and more than 5 million patients have the disease globally.[7,9]

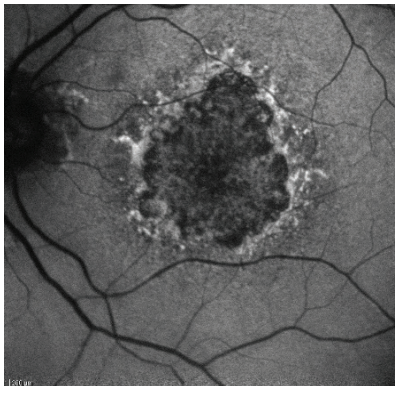

Figure 1. Dense, irreversible scotomas and areas of complete depigmentation of the RPE with sharp margins are hallmark clinical presentations of GA.

Given the age-related nature of the disease, it is unsurprising that increased age is associated with advanced risk—and that longer life expectancies will lead to higher rates of disease. Indeed, prevalence of AMD approximately quadruples every 10 years of age after age 50.[9] Of the 5 million patients with GA globally, 4.4% of them are older than 85, and 22% are over 90.[9]

TABLE 1. AREDS AMD CLASSIFICATION

AREDS Classification/ Category	Defining Features (At Least One Must Be Present)
Category 1 No AMD	• No or a few small drusen (< 63 µm in diameter)
Category 2 Early AMD	• Multiple small drusen (< 63 µm in diameter) • Few intermediate drusen (63-124 µm in diameter) • RPE abnormalities
Category 3 Intermediate AMD	• Extensive intermediate drusen, and at least 1 large drusen (≥ 125 µm in diameter) • GA not involving the center of the fovea
Category 4 Advanced/Late AMD	• Presence of GA involving the fovea and/or • Features of neovascular AMD

Source: Ferris FL 3rd, Davis MD, Clemons TE, et al. A simplified severity scale for age-related macular degeneration: AREDS Report No. 18. *Arch Ophthalmol.* 2005;123(11):1570-1574.
Abbreviations: AMD, age-related macular degeneration; AREDS, age-related eye disease study; GA, geographic atrophy; RPE, retinal pigment epithelium.

CLASSIFICATION OF AMD

AREDS Classification

A number of classification schemes exist for AMD. One of the major contributions of the AREDS was establishing the parameters around detection and classification of AMD. The AREDS classification scheme developed in 2005 divided AMD disease presentation into four categories,[4] the defining features of which are explained in Table 1.

The AREDS classification system can be used to establish a severity score. One severity score point is assigned to each condition in the classification scheme, and both eyes' scores are combined. For example, a patient with drusen and pigment changes in both eyes would have a severity score of 4. A severity score based on the AREDS classification system can be used to

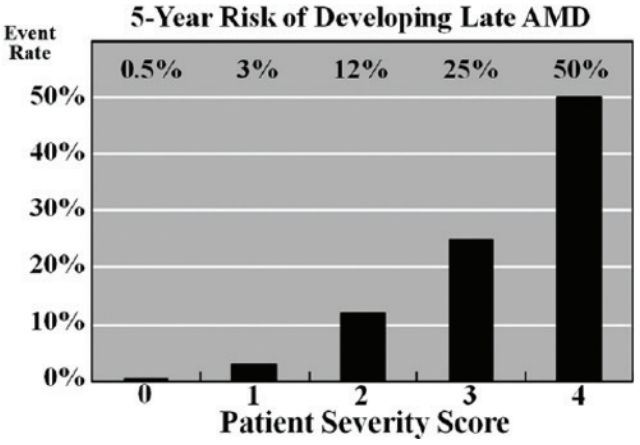

Figure 2. A 5-year risk of developing late AMD can be calculated by using a severity score point system in the AREDS classification scheme.

establish a 5-year risk of progression to late AMD.[4] The risk of 5-year progression vis-à-vis AREDS severity score can be seen in Figure 2. In my experience, patients find this scoring system easy to understand.

Beckman Committee Classification

The Beckman Committee classification system was published in 2013.[3] It is a modified version of the AREDS classification scheme. This system's criteria for disease classification is outlined in Table 2.

The Beckman Committee classification scheme determined that small drusen should be termed drupelets, and that they are normal signs of aging. In this system, the presence of drupelets does not indicate the presence of AMD. Clinically, the Beckman Committee classification system may be used in patients who present with small drusen but no pigmentary abnormalities.

In 2018, the Classification of Atrophy Meetings (CAM) consensus used the Beckman Committee classification scheme to classify atrophy associated with AMD.[10] The list of abbreviations used by the CAM consensus are listed in Table 3. This nomenclature is often used in the setting of a reading center rather than in the clinic.

What is the value of these additional classifications of atrophy? In a recent presentation at EURETINA, a post hoc analysis of the FILLY study demonstrated that pegcetacoplan therapy impacts the progression of nascent GA (eg, iRORA), the earlier stage of disease that precedes atrophy, in areas of the retina outside of GA lesions.[11]

TABLE 2. BECKMAN COMMITTEE CLASSIFICATION

Beckman Committee Classification	Defining Features
No AMD	• No or a few small drupelets (small drusen < 63 µm in diameter) • No RPE pigmentary abnormalities
Early AMD	• Medium drusen (64 µm to 125 µm in diameter) • No RPE pigmentary abnormalities
Intermediate AMD	• 1 large drusen (> 125 µm in diameter) and/or • Any RPE pigmentary abnormalities
Advanced AMD	• GA and/or • Neovascular AMD

Source: Ferris FL 3rd, Wilkinson CP, Bird A, et al. Beckman Initiative for Macular Research Classification Committee. Clinical classification of age-related macular degeneration. *Ophthalmology*. 2013;120(4):844-851.
Abbreviations: AMD, age-related macular degeneration; GA, geographic atrophy; RPE, retinal pigment epithelium.

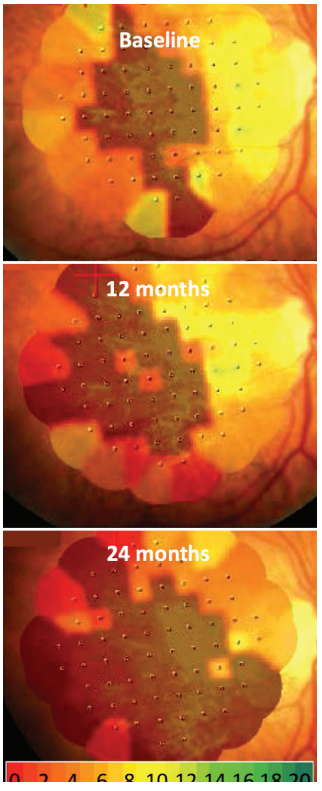

Figure 3. Retinal function in patients with GA can be assessed on microperimetry. Here, a patient's progression can be observed over a 2-year period. These images may be mapped onto fundus photos and compared with imaging reports from other modalities.

QUALITY OF LIFE

Keeping in mind how visual impairment affects patients' lives is paramount to providing care.

Patients with GA find daily living routines disrupted. The inability to dark adapt (ie, transition rapidly from dark to light environments, and vice versa) is among the first complaints I receive from patients with AMD. Impairments to leisure activities (reading, sports), social activities (friendly gatherings, family events) and transportation (ability to drive) often follow.[12] Among patients with GA who have a driver's license, 50% reported discomfort with daytime driving and 88% reported discomfort with nighttime driving.[13]

Patients consider AMD among the most disruptive diseases that could affect quality of life.[14] Patients would prefer to experience myocardial infarction rather than 20/40 VA related to AMD, and have determined that dialysis has a higher quality-of-life score than AMD associated with vision worse than 20/200.

ASSESSEMENTS FOR VISUAL ACUITY

Many retina specialists rely on metrics such as best corrected visual acuity on a Snellen chart and visual acuity score on an Early Treatment of Diabetic Retinopathy Study chart. Amsler grids and contrast sensitivity testing may be used to evaluate

TABLE 3. CAM CONSENSUS CLASSIFICATION OF ATROPHY ASSOCIATED WITH AMD

Term	Abbreviation
Complete RPE and Outer Retinal Atrophy	cRORA
Incomplete RPE and Outer Retinal Atrophy	iRORA
Complete Outer Retinal Atrophy	cORA
Incomplete Outer Retinal Atrophy	iORA

Source: Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: Classification of atrophy report 3 [published correction appears in Ophthalmology. 2019;126(1):177]. *Ophthalmology*. 2018;125(4):537-548.
Abbreviations: AMD, age-related macular degeneration; CAM, classification of atrophy meetings; RPE, retinal pigment epithelium.

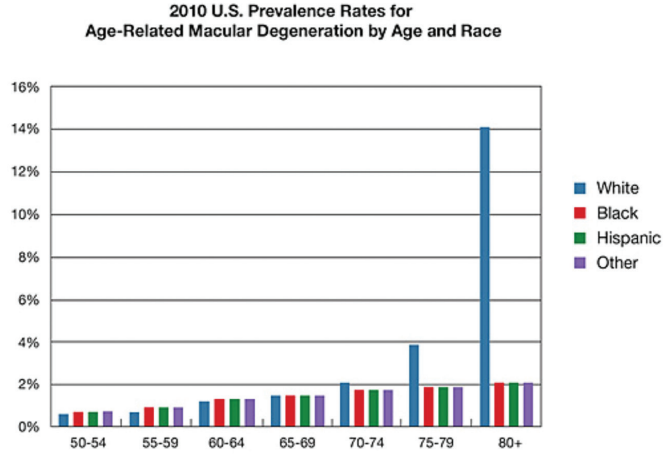

Figure 4. White Americans develop AMD at twice the rate of other racial demographics starting at age 75, and at nearly 14 times the rate of other racial demographics starting at age 80.

quality of vision in some patients. Reading speed tests may assist in evaluating functional vision.

Microperimetry is used to measure retinal function in eyes with GA (Figure 3).[15] Functional progression of GA and area of scotomas can be evaluated on microperimetry. Visual sensitivity can be mapped to a fundus photo and compared with images attained with other modalities. In this modality, stimuli can be used to identify very specific areas of the retina where the patient has functional issues.

RISK FACTORS

As one might expect with an age-related disease, aging is the leading risk factor for developing advanced AMD and GA.[8] Factors outside of patient control include gender, family history, and genetic predisposition.[8]

Smoking and diet, however, are two factors that patients can control. Smoking history and status as a current smoker are associated with increased risk of AMD progression.[16] Smokers are more likely than nonsmokers to develop GA.[17] Patients consuming a Mediterranean diet (ie, nutrient-rich foods such as fruits, vegetables, legumes, and fish) have reduced risk for advanced AMD.[18]

White Americans develop AMD at a significantly higher rate than other demographics starting at age 75 (Figure 4).[8] Ocular factors such as aphakia and hyperopia and systemic factors such as cardiovascular disease are also risk factors for AMD development.[19]

CONCLUSION

An understanding of the pathophysiology of AMD and GA may help clinicians understand the disease, and knowing how the disease affects patients' quality of life can guide treatment decisions. Included in this series, Nathan Steinle, MD, explores GA's pathophysiology and natural history on page 8, and Charles C. Wykoff, MD, PhD, details treatment options and pipeline drug candidates on page 12. ■

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PATHOPHYSIOLOGY AND NATURAL HISTORY OF GA

A review of data shows us what we know about the course of this blinding disease.

BY NATHAN STEINLE, MD

By better understanding the pathophysiology of geographic atrophy (GA), clinicians and researchers can build strategies for treatment.

PATHOPHYSIOLOGY OF GA

In patients with GA, complement deposition between the retinal pigment epithelium (RPE) and Bruch membrane occurs,[1] followed by a loss of complement regulation and a breakdown of the blood-retinal barrier.[2]

Drusen, which are extracellular deposits of lipid- and protein-rich debris, are the first clinically detectable evidence of age-related macular degeneration (AMD).[2] RPE secretions are a major source of drusen.[3] Drusen are approximately 40% lipid, along with lipofuscin, albumen, immunoglobulins, and amyloid.[2] Complement factors C1q, C3, C5, and C5b–9 have also been detected in drusen.[2]

The RPE is essential to maintaining a healthy retina. The RPE facilitates the transportation of nutrients to photoreceptor layers, phagocytizes waste, and is a source of tropic factors such as VEGF-A.[2] The RPE also maintains the integrity of the outer retinal blood barrier and produces pigment to absorb scattered light.[2]

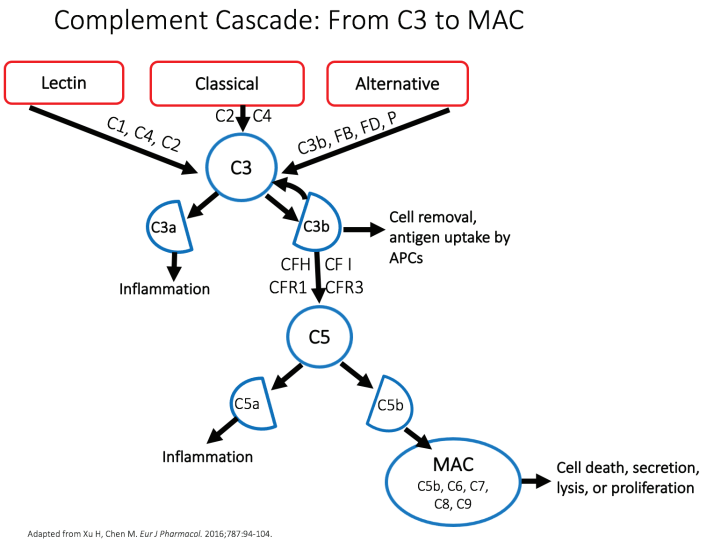


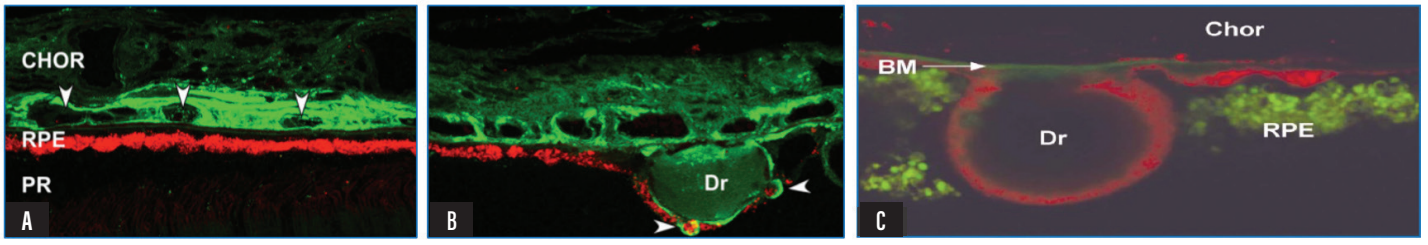
Figure 1. Any of the three complement pathways activate C3, leading to a cascade that results in the creation of MAC. Approximately 30 proteins are involved in this cascade.

The Complement Cascade

The complement cascade is part of the immune system involved in detection and removal of foreign pathogens. Research suggests that overactivation of the complement cascade may contribute to the development of AMD via inflammation, phagocytosis, and the creation of membrane attack complex (MAC).[4]

Three pathways activate the complement cascade: the classical pathway, the lectin pathway, and the alternative pathway (Figure 1). All three of these pathways activate C3, leading to the activation of (in order) C3b, C5, and C5b, which in turn leads to the creation of MAC.[4] Cell death occurs in the presence of MAC. Researchers' understanding of the complex nature of the complement system—it involves approximately 30 proteins—is growing, and it may serve as a useful target for GA therapy.

Staining for C3 and C5 beneath the RPE and in drusen on confocal immunofluorescence microscopy illustrates the degree to which deposits accumulate in patients with GA (Figure 2).[5,6] This anatomic imaging data supports the claim that complement activation is involved in the progression of GA.



Abbreviations: BM, Bruch's membrane; CHOR, choroid; Dr, drusen; RPE, retinal pigment epithelium; PR, photoreceptor layer

Anderson DH, Mullins RF, Hageman GS, et al. *Am J Ophthalmol.* 2002;134(3):411-31
Anderson DH, Radeke MJ, Gallo NB, et al. *Prog Retin Eye Res.* 2010;29:95-112.

Figure 2. Confocal immunofluorescence microscopy illustrates the degree to which C3 and C5 accumulate in the sub-RPE space and in drusen. C3 is illuminated in green in Figure 2A and 2B, and C5 is illuminated in red in Figure 2C.

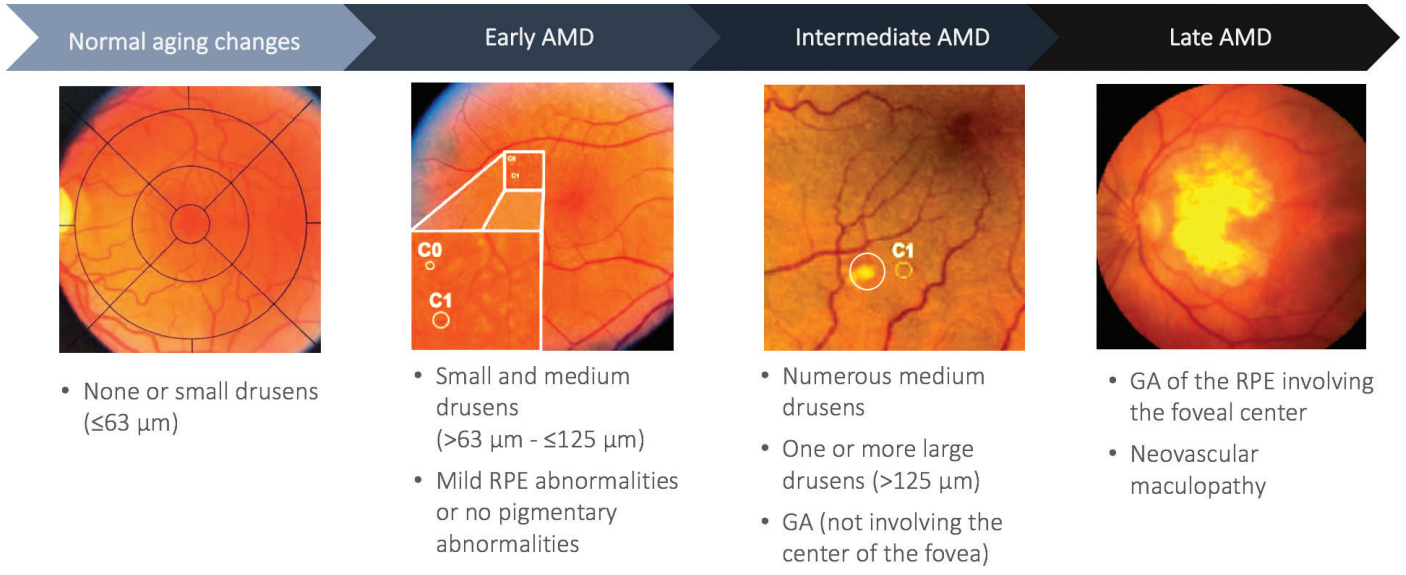


Figure 3. CFP can be used to image patients with GA at all stages of disease. CFP's ability to follow drusen makes it a particularly useful tool for classifying disease severity and for tracking progression.

Genetic Factors

The risk alleles *CFH* and *ARMS2* appear to share a common pathway in the pathogenesis of AMD.[7] These two risk alleles are independently associated with complement activation. Activation of the alternative pathway; elevated levels of C3d, C5a, and complement factor B; and increased ratios of C3d to C3 are all associated with AMD.[7]

Approximately 40 genes are implicated in development of GA, accounting for about 50% of the overall risk of development of advanced disease.[8,9] Researchers have noted complement factor H's association with AMD development,[10] along with complement factor B, complement factor I, C2, C3, and C9.

CLINICAL PRESENTATION OF GEOGRAPHIC ATROPHY

Clinically, GA presents as round or oval patches of atrophy of the retina, RPE, and underlying choroid.[11,12] In some cases, patches grow in size and number; in other cases, patches join together to become larger atrophic lesions. Although GA tends to be bilateral, asymmetric cases are common.

Several modalities are useful for imaging patients with GA. These include fundus color photography (CFP), fundus autofluorescence (FAF), and optical coherence tomography (OCT).

Color Fundus Photography

CFP is easy to obtain, is noninvasive, and is a practical tool for imaging patients with early AMD.[13] Drusen and pigmentary abnormalities can be detected on CFP, and lesion size in GA patients can be evaluated on CFP (Figure 3).[14] Circular lesions with demarcated edges that occur alongside partial or complete depigmentation of the RPE are hallmarks of GA lesions.[15] Because CFP may be used to evaluate drusen size and volume and the presence of GA lesions, it is an effective imaging modality for clinicians who employ the Age-Related Eye Disease Study classification system[16] or the Beckman Committee classification system,[17] both of which were discussed in the preceding article by Rishi P. Singh, MD.

Fundus Autofluorescence

FAF may be used to track GA growth and the extent of RPE damage, and to map areas of lipofuscin deposits, which are autofluorescent in nature. GA lesions themselves are hypoautofluorescent.[13]

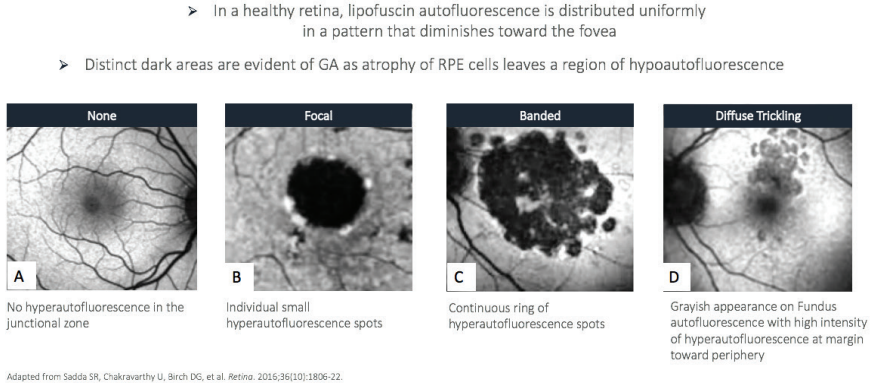


Figure 4. (A) A healthy retina shows a uniformly distributed pattern of hyperautofluorescent spots. (B) Focal patterns show hyperautofluorescent spots on the border of a GA lesion. (C) Banded patterns of hyperautofluorescent spots encircling GA lesions are sometimes observed, as are less-defined patterns of GA lesions and hyperautofluorescent material (D).

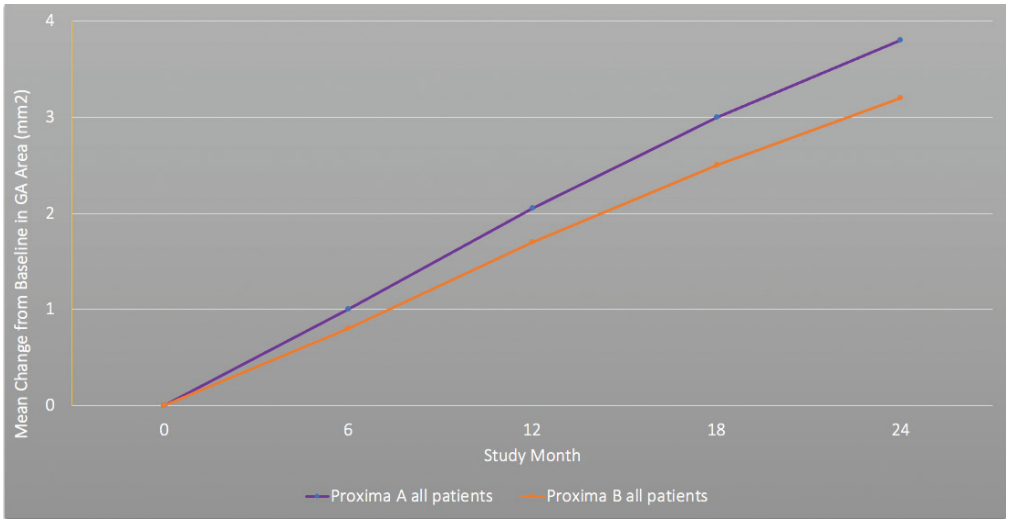


Figure 5. The Proxima A and Proxima B studies found that mean GA lesion area grew over the course of 2 years.

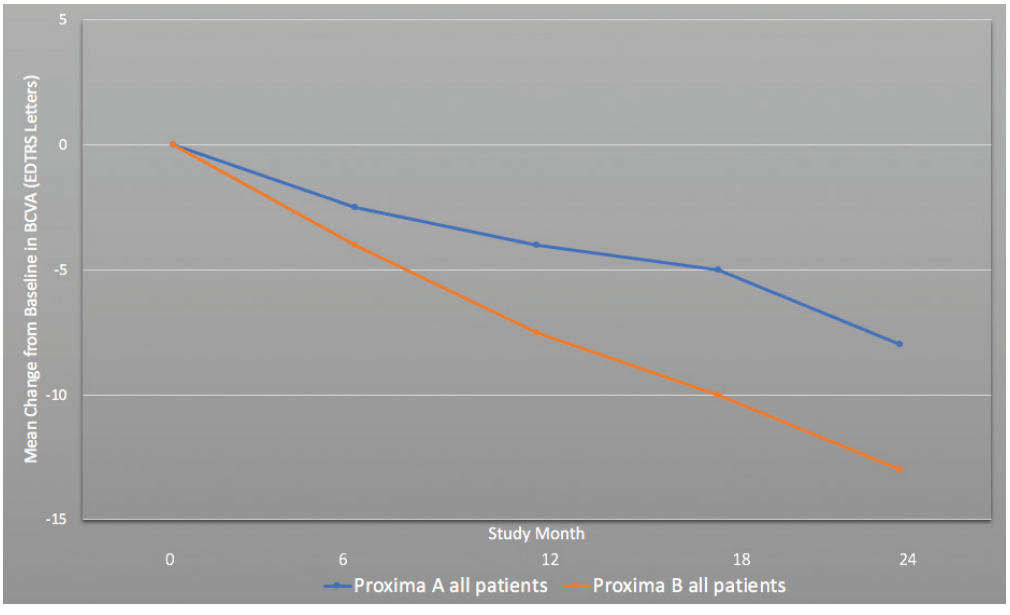


Figure 6. The Proxima A and Proxima B studies found that patients lost significant vision over 2 years.

TABLE. HYPERAUTOFLUORESCENT PATTERNS OF LIPOFUSCIN ADJACENT TO GA LESIONS MAY HELP PREDICT THE RATE OF GA PROGRESSION.

Hyperfluorescent pattern	Median GA lesion enlargement rate per year
Focal	0.81 mm^2
Banded	1.81 mm^2
Diffuse Trickling	3.02 mm^2
Overall	1.52 mm^2

Source: Holz FG, Bindewald-Wittich A, Fleckenstein MD, et al. FAM-Study Group. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. *Am J Ophthalmol.* 2007;143(3):463-472.

In a healthy retina, lipofuscin autofluorescence is distributed uniformly in a pattern that diminishes toward the fovea. No hyperautofluorescent material is observed in the junctional zone (Figure 4A). Focal lipofuscin patterns are observed in some patients as small, individual hyperautofluorescent spots on the periphery of a GA lesion (Figure 4B). A pathophysiologic change is likely to occur near those spots. GA lesions surrounded by a continuous line of hyperautofluorescent lipofuscin are called banded patterns (Figure 4C). The term diffuse trickling is used to describe cases of GA that do not have sharp lesion borders but show evidence of hyperautofluorescent lipofuscin graded patterns (Figure 4D).

Classification of FAF perilesional patterns inform clinicians about a GA patient's likely progression,[18,19] ie, which focal, banded, and diffuse GA patterns increase the likelihood of GA progression. Findings from Holz et al are outlined in the Table.[18]

Optical Coherence Tomography

OCT imaging detects AMD-related damage to the retina by depicting loss of RPE and choriocapillaris.[20] Loss of photoreceptors occurs with GA advancement, and the diffuse thinning associated with GA can be observed on OCT.[21] The specificity of OCT matches that of CFP for detecting atrophy.[22]

NATURAL HISTORY

The Proxima A and Proxima B studies observed patients with GA for 2 years.[23] Mean change in GA area increased during the 2-year period (Figure 5). Best corrected visual acuity results steadily declined for these patients, with patients in Proxima A losing approximately 13.9 letters at 24 months (Figure 6).[23]

At 24 months, patients in Proxima A and Proxima B lost approximately 7.6 to 8.4 letters of low-luminance visual acuity (LLVA).[23] Low luminance deficit (calculated by subtracting LLVA from BCVA) fell by approximately 5.8 letters in Proxima A and by 1.8 to 4.0 letters in Proxima B.

BIGGEST RISK FACTORS FOR PROGRESSION OF GEOGRAPHIC ATROPHY

Patients with large baseline lesions and multifocal lesions are more likely to experience GA progression compared with patients without such baseline characteristics.[24] Patients with FAF lipofuscin patterns categorized as banded or diffuse trickling are more likely to experience GA progression compared with those who have no evidence of lipofuscin or focal patterns on FAF.[24] Patients with extrafoveal lesions are likely to experience progression into the periphery and are more likely to progress at faster rates than those with subfoveal lesions.[24]

CONCLUSION

There is no therapy approved by the US FDA for the treatment of GA. However, a number of pipeline candidates are under investigation. Charles C. Wykoff, MD, PhD, details those on page 12. ■

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THE GEOGRAPHIC ATROPHY PIPELINE

Successful targeting of the complement cascade appears to be emerging as an effective therapeutic option for patients.

BY CHARLES C. WYKOFF, MD, PHD

Many retina specialists would argue that nonexudative age-related macular degeneration (AMD) and geographic atrophy (GA) are the largest unmet needs in the clinic. There are no commercially available therapies for this disease despite numerous attempts from innovators to have a drug reach a phase 3 primary endpoint. Still, a number of drug candidates are in the pipeline. We will review past and current drug candidates here.

As Nathan Steinle, MD, explained earlier in this series, the complement cascade may be an effective target for GA therapy. A series of trials have attempted to intervene at the complement level.

SHOTS ON GOAL, BUT NO SUCCESS

In 2013, the investigator-sponsored COMPLETE study explored whether intravenous infusion of the anti-C5 monoclonal antibody eculizumab would affect the rate of GA growth in approximately 30 patients who were actively treated over 24 weeks. Patients in the treatment group did not experience a significantly different rate of GA growth compared with sham.

LFG316 is a monoclonal antibody that targets C5. In 2016, investigators found that LFG316 did not significantly reduce GA lesion size or improve visual acuity in approximately 150 patients.[1]

Lampalizumab is an antibody fragment targeting complement factor D, which is the rate-limiting enzyme of the alternative complement pathway, upstream of C3. In the phase 3 Chroma and Spectri trials, 1,881 patients were assigned to receive treatment or sham every 4 or 6 weeks. In 2017, researchers announced that at 1 year, no significant differences were observed in GA lesion area growth among trial's two intervention arms compared with the pooled sham arms.[2]

A PROMISING PIPELINE

Several drug candidates have shown potential to have a therapeutic effect.

Pegcetacoplan

Pegcetacoplan is pegylated, highly selective, bicyclic peptide that prevents C3 cleavage into C3a and C3b. Reduction of C3b, in turn, leads to cessation of the complement cascade from propagating downstream, and also results in decreased levels of C5a and C5b, which can function as inflammatory mediators.

The safety and efficacy of pegcetacoplan was evaluated in the single-masked phase 2 FILLY trial. Patients were randomly assigned to 15 mg pegcetacoplan or sham monthly or 15 mg pegcetacoplan or sham every other month (EOM). The primary endpoint of reduction in growth of GA area was assessed at 12 months, and the total duration for the trail was 18 months. Neither drug nor sham were administered between months 12 and 18.

In FILLY, patients who were dosed with pegcetacoplan monthly or EOM had a reduction in GA growth at 1 year compared with sham (Figure 1).[3] Patients in the monthly arm had a 29% reduction (P = .008) and those in the EOM had a 20% reduction (P = .067); the prespecified P value in FILLY was 0.1.

Patients in FILLY who had bilateral GA received treatment in only one eye. In these patients, researchers compared fellow eyes to study eyes (Figure 2). At 12 months, no differences were detected in the sham groups between eyes that received sham treatment and fellow eyes. A 10% (P > .1) difference in GA lesion growth was detected in eyes that received EOM pegcetacoplan treatment compared with fellow eyes. In eyes that received monthly pegcetacoplan therapy, the difference was 23% (P = .083) between pegcetacoplan treated and fellow eyes.[3]

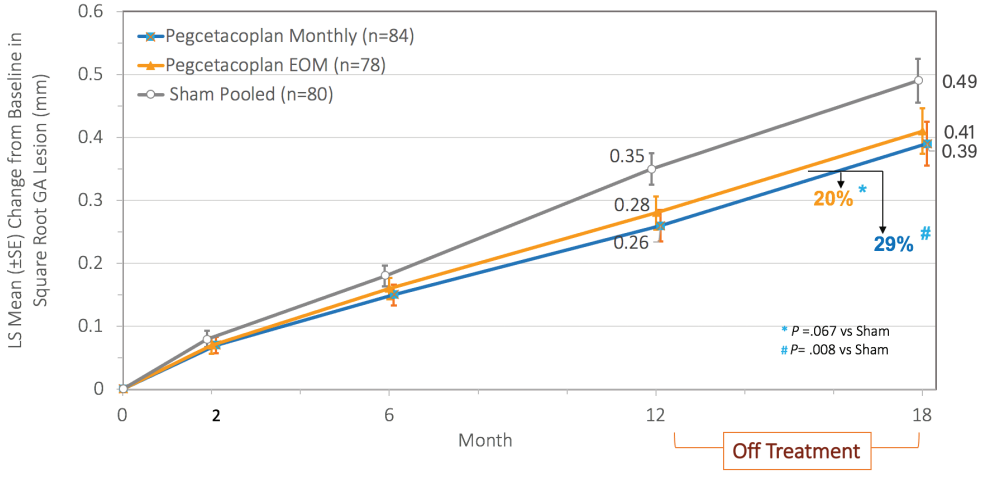

Figure 1. The phase 2 FILLY study found that GA lesion growth at 1 year was reduced by 29% and 20% in patients who were treated with pegcetacoplan monthly or EOM, respectively, compared with sham. Both reductions were statistically significant.

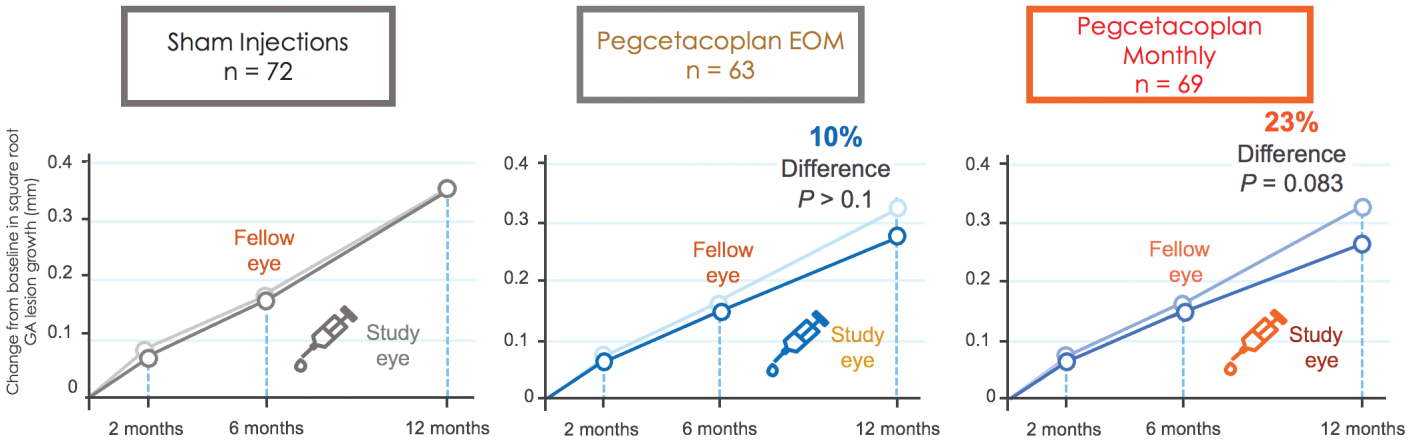

Figure 2. Patients with bilateral GA at baseline who received treatment monthly with pegcetacoplan experienced a 23% difference in GA lesion growth at 1 year compared with their untreated contralateral control eye.

During the first 6 months of the FILLY study, patients in all groups experienced the same rate of GA lesion growth. During the second 6 months of the study, a 33% (P = .01) difference was noted in the EOM group compared with sham, and a 47% (P < .001) difference was noted in the monthly group. During the final 6 months of the study (during which no intervention was given), differences of 9% and 12% were detected in the EOM and monthly groups compared with sham; neither value was statistically significant.[3]

No difference in visual acuity was noted at the 12- or 18-month endpoints in FILLY.[3] Decline of visual acuity at a rate of approximately 1 line per year is consistent with data from the GA natural history studies Proxima A and B.[4] It should be noted that the study investigators enrolled patients with GA lesions that could be either foveal-involving of nonfoveal-involving.

Development of exudative AMD at 18 months occurred in 10.5% of patients. A dose-dependent relationship with pegcetacoplan exposure and the development of investigator-determined exudative AMD development was observed, as 1% of sham patients, 9% of EOM patients, and 21% of monthly patients showed evidence of exudative AMD at 18 months. Patients with exudative AMD in the contralateral untreated eye were more likely to experience bilateral exudative AMD at 18 months than patients without contralateral exudative AMD.

The DERBY and OAKS trials, two multinational phase 3 trials assessing the safety and efficacy of pegcetacoplan for the treatment of GA are fully enrolled and primary results at 12 months are expected in 2021.

Avacincaptad Pegol

Avacincaptad pegol works further downstream than pegcetacoplan to inhibit cleavage of C5, preventing the accumulation of C5a and C5b and the resulting creation of MAC. Avacincaptad is a pegylated 39-base RNA aptamer.

A double-masked, phase 2b/3 clinical trial (retroactively named the GATHER1 trial) assessing the safety and efficacy of avacincaptad for the treatment of GA was divided into two parts

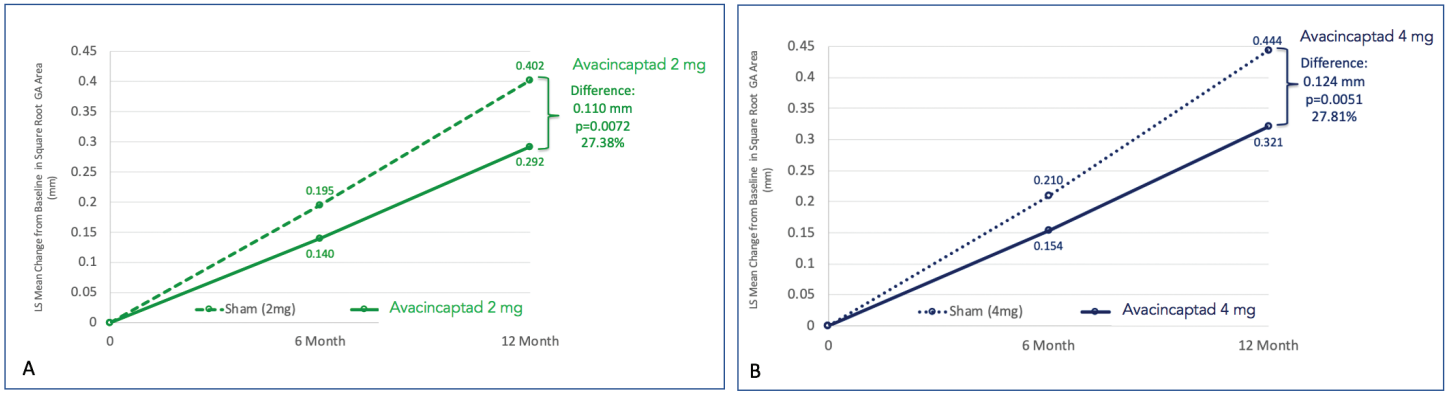

Figure 3. Both parts of a phase 2 study evaluating the safety and efficacy of avacincaptad for the treatment of GA found that monthly therapy of 2 mg (A) and 4 mg (B) significantly reduced GA growth rate.

(parts 1 and 2), with a total of 286 patients among all arms. In part 1, patients received either 1 mg or 2 mg avacincaptad monthly or sham. In part 2, patients received 2 mg avacincaptad plus sham each month, two doses of 2 mg avacincaptad each month (totaling 4 mg avacincaptad each month), or two doses of sham. The primary endpoints in both study parts were 12 months.[5]

At 12 months, in part 1, patients who received monthly 2 mg avacincaptad therapy each month experienced a 27% reduction in GA growth area at 1 year compared with sham ($P = .007$) (Figure 3). In part 2, patients who received 4 mg total of avacincaptad (ie, two doses of 2 mg avacincaptad) each month experienced a 28% reduction in GA growth area at 1 year ($P = .005$).

From a safety perspective, sham treatment was associated with a 2.3% rate of new-onset neovascular AMD compared with rates of 9.0% and 9.6% in the 2-mg and 4-mg arms, respectively. It should be noted that unlike the FILLY study, GATHER1 did not enroll patients with a history of neovascular AMD in the fellow eye or patients with foveal-involving GA at baseline.

A multicenter, phase 3 study, GATHER2, is currently enrolling approximately 400 patients and will randomly assign them to monthly 2 mg avacincaptad or sham. The primary endpoint will be assessed at 12 months.

MORE CANDIDATES

A multitude of additional therapeutic options are being investigated in earlier stage clinical trials which are pursuing both complement and noncomplement targets.

NGM621

NGM621 (NGM Biopharmaceuticals) is a humanized IgG1 monoclonal antibody with a high affinity for binding to C3. It differs from pegcetacoplan in that it is not pegylated. In a phase 1 open-label study, no safety signals were detected.[6] The ongoing multicenter, phase 2 CATALINA trial will evaluate the efficacy and safety of intravitreal injections of NGM621 compared with sham.[6] Patients will receive 48 weeks of NGM621 or sham every 4 or 8 weeks.

GT005

In 2015, Kavanagh et al found that physiologically low serum levels of complement factor I (CFI) may be associated with increased risk of advanced AMD.[7] GT005 is an AAV-based gene therapy delivered via subretinal injection designed to induce expression of CFI.

The phase 2 EXPLORE study is examining the safety and efficacy of GT005 in patients with GA with CFI mutations.[8] The treatment group will receive two doses and will be compared with untreated controls. A forthcoming phase 2 study called HORIZON will examine GT005 in patients with and without CFI mutations, and will employ a structure similar to EXPLORE.

GEM103

GEM103 is a native, fully functional recombinantly manufactured full-length complement factor H (CFH) that is identical to endogenous CFH. It is delivered via intravitreal injection. A phase 1 study has been completed.[9] The 6-month phase 2 REGATTA study will examine the therapy in patients randomly assigned to monthly or EOM therapy.

CONCLUSION

Several promising candidates are in the pipeline for the treatment of GA. It should be noted that drug candidates discussed in this article do not represent an exhaustive examination of drugs in development, and there are other promising agents in earlier stages of development. ■

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CASE DISCUSSION

This discussion summarizes a case presentation and audience question-and-answer session with the panelists during a recent webinar.

BY RISHI P. SINGH, MD; NATHAN STEINLE, MD; AND CHARLES C. WYKOFF, MD, PHD

Esther is an 88-year-old Hispanic woman with 20/30 VA in her right eye, with which she has difficulty reading. In her left eye, she has count fingers vision and an advanced brunescent cataract. Pigmentary changes and atrophy were detected on examination in both eyes (Figure). Esther is visiting your clinic for the first time based on a referral from a cataract surgeon who wants your opinion on whether cataract surgery should be performed on her left eye.

DR. SINGH: The images in the Figure, particularly the OCT enface infrared images, are useful in a situation like this. Central atrophy is obvious in the left eye. The right eye has a small island of preserved retinal pigment epithelium cells centrally.

DR. WYKOFF: In cases such as this, I almost always get OCT imaging and color fundus photography at baseline. Sometimes I will also order fundus autofluorescence (FAF) and a fluorescein angiogram if I suspect neovascularization is present.

I am surprised that this patient can see 20/30 given the severity of her geographic atrophy (GA) in her right eye. Age-related macular degeneration (AMD) as presented here can be frustrating, as the paracentral GA in her right eye will likely progress. If future therapies can prevent GA growth in a patient like this, it would be very clinically useful.

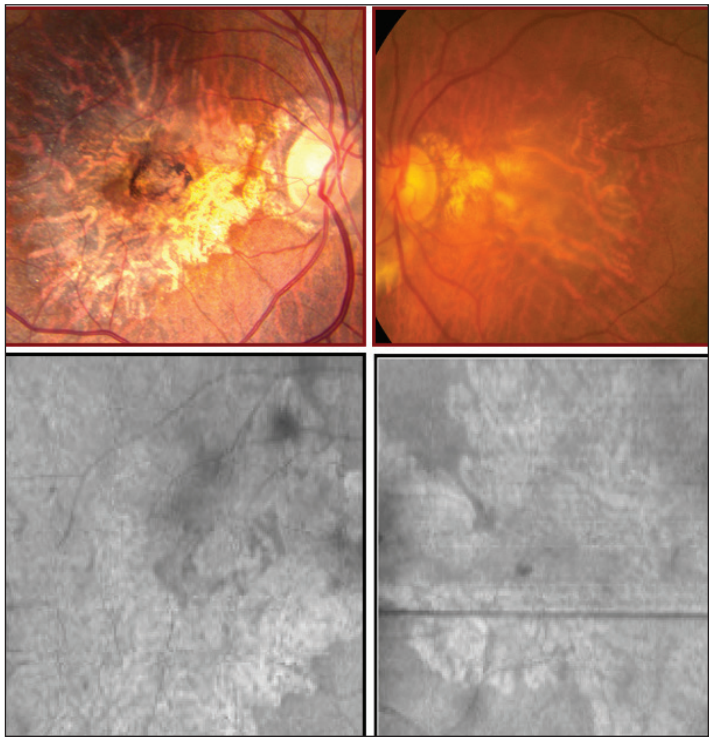

Figure. Pigmentary changes and atrophy are detected in both eyes; the patient had a brunescent cataract in her left eye.

DR. STEINLE: AMD cases like this are difficult to predict regarding cataract surgery. Cataract surgery may result in some improved peripheral vision in the left eye; however, the central GA will limit the best corrected vision in the left eye. Patients like Esther may have a sense of false hope that cataract surgery will significantly improve their vision but given the foveal involvement of her GA in the left eye, that seems unlikely.

Having Esther's caregiver in the room with her during the exam will be useful, as he or she will need to understand how Esther's condition will progress over time. In cases like this, FAF imaging is very helpful and easy to understand for both the patient and for caregivers.

DR. WYKOFF: It's important to remember that patients like Esther are frightened when they visit your office. Patients often think that they are going to be totally blind as their disease advances. I try to clarify the natural history of the disease process and reassure them that this process will very likely not lead to complete blindness.

DR. SINGH: Would you recommend cataract surgery in this patient?

DR. STEINLE: Yes, I would. I would try to limit expectations, but I would still proceed. I inform the patient that I expect cataract surgery to make everything "lighter and brighter" in the left eye, but that central vision will remain compromised.

DR. WYKOFF: In many cases, eyes like this can experience substantial functional improvement.

DR. SINGH: I agree—I've seen some of these patients gain up to 10 letters of vision. It's also important to remember that visual function and patient satisfaction are not just measured by

Snellen visual acuity. Our lab at the Cleveland Clinic, in fact, has a publication pending that evaluates visual outcomes in patients with various levels of AMD. Even patients with center-involving GA have significant improvements in vision.

Q | What do you tell a patient with extensive GA who has 20/30 VA and wants to drive?

DR. WYKOFF: I encounter this situation often. I tell patients that I'm not going to take away their driver's license, but that they are probably not safe to drive. I suggest that they rely on caregivers for transportation. Reminding patients that I as a retina specialist am not a primary eye care provider is useful in this situation. I advise that they return to their optometrist or general ophthalmologist, where formal visual fields and refractions can be performed, to manage this important issue.

DR. SINGH: This is a difficult topic, as our patients value their independence. I sometimes use humor—"I bet you're a better driver who gets fewer tickets than I do"—to defuse the discomfort of delivering bad news. I frame my response as a safety issue, and our patients generally respond well to that framework.

Q | Some of the drug candidates for GA that you mentioned in your presentations could be approved for dosing every 1 or 2 months. How do you think this will work in the real world?

DR. STEINLE: It's important to recognize the structure of pipeline trials. Take as an example the DERBY and OAKS trials for pegcetacoplan. These phase 3 GA trials employ monthly and every-other-month dosing arms. If we end up seeing a dose-dependent response in those trials, then we'll likely dose patients monthly. I'm not sure we will employ treat-and-extend regimens with any of the GA candidates in the pipeline. If that is the case, our clinics will face the challenge of a massive increase in patient volume as monthly GA patients begin to receive treatment alongside our treat-and-extend, as-needed, and monthly wet age-related macular degeneration patients, diabetic eye disease patients, and retinal vein occlusion patients.

DR. SINGH: Every retina specialist is a tinker, and I suspect that if drugs to treat GA are granted regulatory approval for monthly administration, that we will shortly thereafter see clinical trials that examine the possibility of longer durations of administration. Dr. Wykoff worked on the TREX trial, which examined this exact question in wet AMD therapy.[1]

DR. WYKOFF: If the medications in clinical trials are proven safe and effective in the ongoing clinical development programs, additional work may be able to identify clinical and/or genetic factors that may be able to predict response and determine optimal retreatment intervals.

Q | How will we select which patients are best suited for GA therapy?

DR. STEINLE: FAF may be key in determining which GA patients are most likely to benefit from intervention. Patients with hyper-autofluorescence at the lesion border are most likely to experience lesion growth—and those patients are most likely to receive a benefit from a therapy designed to slow that growth in GA.

DR. WYKOFF: Given the current inclusion and exclusion criteria for the ongoing phase 3 trial programs, we will not know how effective these drugs will be in patients without hyperfluorescent borders on FAF. Additional studies will need to be performed in order to learn how eyes with different phenotypes, such as no hyperfluorescence at the GA border, will perform.

Lesion location may be key, too. Patients with foveal-involving lesions may be too far gone, as intervention at this point is not designed to arrest or reverse growth. It is only designed to slow growth. ■

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Full Name_____

Phone (required) _____ Email (required) _____

Address/P.O. Box _____

City _____ State/Country____ Zip/Postal Code_____

License Number _____ OE Tracker Number _____

DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
___ 51+

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Describe the prevalence of AMD and classify by severity: early, intermediate, and advanced (ie, wet AMD and GA)	_____	_____	_____
Explain the pathogenesis of GA	_____	_____	_____
Distinguish which imaging modalities are best suited for GA evaluation	_____	_____	_____
Categorize new therapies in the pipeline for GA	_____	_____	_____
Evaluate the functional and anatomic outcomes used in managing patients with GA	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to distinguish which imaging modalities are best suited for geographic atrophy (GA) evaluation (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. According to the Age-Related Eye Disease Study (AREDS), what percentage of patients in the highest risk category for macular degeneration progressed to central GA?

a. 24.6%
b. 30.8%
c. 42.7%
d. 53.9%

3. Which of the following statements about GA is NOT true:

a. GA accounts for ~35% of all advanced age-related macular degeneration (AMD) cases
b. GA accounts for 20% of all legal blindness attributed to AMD
c. Prevalence of GA increases with age
d. The AREDS study showed a higher risk of progression to neovascular AMD than GA in patients with high risk macular degeneration

4. Which of the following is the description of Intermediate AMD (Category 3) according to the AREDS study?

a. Presence of GA involving the fovea and/or features of neovascular AMD
b. Multiple small drusen, few intermediate drusen, RPE abnormalities
c. Extensive intermediate drusen, and at least one large drusen; GA not involving the center of the fovea
d. None or few small drusen

5. All of the following are risk factors that lead to advanced AMD and GA EXCEPT:

a. Aging
b. Family History
c. Smoking
d. Genetic predisposition and diet
e. High intraocular pressure

6. Which of the following statements about risk factors for AMD is true?

a. Females are at higher risk of developing AMD than males
b. Males are at higher risk of developing AMD than females
c. Smoking is not a significant risk factor for AMD
d. Increasing age is not a significant risk factor for AMD

7. Which of the following is NOT a function of the retinal pigment epithelium?

a. Brings nutrients to the photoreceptor layer
b. Recycles photoreception waste through phagocytosis of photoreceptor outer segments
c. Maintains the integrity of the outer blood-retinal barrier through tight junctions
d. Maintains a dense network of blood vessels to supply oxygen and nutrients to the outer retina

8. Which of the following imaging modalities can visualize the distribution of lipofuscin to allow a mapping of the size of GA?

a. Fundus color photography
b. Fundus autofluorescence
c. Optical coherence tomography
d. B-scan ultrasonography

9. Which pattern of hyperautofluorescence on fundus autofluorescence imaging is linked with strong evidence of higher rate of GA progression?

a. None
b. Focal
c. Diffuse trickling

10. You are seeing Ms. Smith for a routine eye exam. She is a 65-year-old white woman who has recently noticed difficulty focusing. On exam, you note one drusen, approximately 140 microns in diameter, along with retinal pigment epithelium abnormalities. Which of the following is the best statement to counsel this patient?

a. You have mild early changes consistent with early macular degeneration. I do not recommend any treatment.
b. You have mild early changes consistent with early macular degeneration. I recommend you start using an Amsler Grid.
c. You have changes consistent with intermediate macular degeneration. I do not recommend any treatment.
d. You have changes consistent with intermediate macular degeneration. I recommend you start AREDS2 supplementation, avoid smoking, use sun protection, and monitor for further changes using an Amsler Grid.

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____

This activity improved my competence in managing patients with this disease/condition/symptom. _____ Yes _____ No

Probability of changing practice behavior based on this activity: _____ High _____ Low _____No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

Change in pharmaceutical therapy _____

Change in nonpharmaceutical therapy _____

Change in diagnostic testing _____

Choice of treatment/management approach _____

Change in current practice for referral _____

Change in differential diagnosis _____

My practice has been reinforced _____

I do not plan to implement any new changes in practice ___

Please identify any barriers to change (check all that apply):

_____ Cost

_____ Lack of consensus or professional guidelines

_____ Lack of administrative support

_____ Lack of experience

_____ Lack of time to assess/counsel patients

_____ Lack of opportunity (patients)

_____ Reimbursement/insurance issues

_____ Lack of resources (equipment)

_____ Patient compliance issues

_____ No barriers

Other. Please specify: _____

_____

_____

The design of the program was effective for the content conveyed. ___ Yes ___ No

The content supported the identified learning objectives. ___ Yes ___ No

The content was free of commercial bias. ___ Yes ___ No

The content was relative to your practice. ___ Yes ___ No

The faculty was effective. ___ Yes ___ No

You were satisfied overall with the activity. ___ Yes ___ No

Would you recommend this program to your colleagues? ___ Yes ___ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

_____ Patient Care

_____ Practice-Based Learning and Improvement

_____ Professionalism

_____ Medical Knowledge

_____ Interpersonal and Communication Skills

_____ System-Based Practice

Additional comments:

_____

_____ I certify that I have participated in this entire activity.

This information will help evaluate this CME activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address: _____

_____