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Contemporary Management of Geographic Atrophy: Evolving Approaches to Diagnosis, Characterization, and Therapy

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Contemporary Management of Geographic Atrophy: Evolving Approaches to Diagnosis, Characterization, and Therapy

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Content Source

This continuing education (CE) activity captures content from a live-virtual symposium.

Activity Description

This supplement summarizes a live-virtual symposium on the treatments for geographic atrophy (GA) that are expected to reach the market in the near future. These experts review the identification of GA lesions and other important aspects of patient care prior to referral to a retina specialist for administration of therapy.

Target Audience

This certified CE activity is designed for optometrists.

Learning Objectives

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

- **Summarize** the prevalence of age-related macular degeneration and GA and define the burden of illness linked specifically to GA
- **Comprehend** and **explain** the pathogenesis of GA
- **Describe** GA disease detection and factors influencing progression
- **Appraise** the therapies targeting GA that have previously been explored
- **Articulate** the most important data related to drug candidates in the pipeline, with a special emphasis on those candidates furthest along in development

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PRETEST QUESTIONS

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

1. Please rate your confidence in your ability to comprehend and explain the pathogenesis of geographic atrophy (GA) (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. All of the following are Classification of Atrophy Meetings (CAM) criteria for diagnosing complete retinal pigment epithelial (RPE) and outer retinal atrophy EXCEPT?

A. Region of hypertransmission ≥ 250 µm in diameter
B. RPE zone of attenuation/disruption ≤250 µm in diameter
C. Evidence of overlying photoreceptor degeneration
D. Absence of scrolled RPE or other signs of an RPE tear

3. A 65-year-old woman presents to your office for routine eye exam. On exam, you note a few drusen >125 mm in her right eye, with pigmentary abnormalities in her left eye. What stage of age-related macular degeneration (AMD) does she have?

A. Early AMD
B. Intermediate AMD
C. Severe AMD
D. Advanced AMD

4. Your 78-year-old patient with AMD presents for follow-up. You note bilateral large drusen >125 mm on exam primarily in the fovea. On fundus autofluorescence, you note these lesions have a banded GA lesion border pattern. You also note the presence of reticular pseudodrusen. All of the following are risk factors for progression of AMD in this patient, EXCEPT?

A. Larger baseline lesions size
B. Foveal lesion location
C. Presence of reticular pseudodrusen
D. Banded/diffuse GA lesion border patterns

5. All of the following are suitable tests to assess GA progression, EXCEPT:

A. Contrast sensitivity measurement
B. Dark adaptation
C. Reading speed
D. Best corrected visual acuity

6. A 75-year-old patient presents to your office for evaluation. You note bilateral AMD pigmentary abnormalities, but an otherwise normal exam. What stage of AMD does this patient have?

A. No AMD
B. Early AMD
C. Intermediate AMD
D. Advanced AMD

7. What is the approximate prevalence of people worldwide affected by late-stage dry AMD (GA)?

A. ~ 2 million
B. ~ 5 million
C. ~ 7 million
D. ~ 10 million

8. What is the greatest risk factor for AMD?

A. Aging
B. Diet high in saturated fat
C. History of excessive sun exposure
D. Male sex

9. All of the following statements about the genetic risks for AMD are true, EXCEPT?

A. The key genes linked to AMD/GA involve the immune/complement systems
B. Genes linked to increased AMD risk are implicated in decrease of reactive oxygen species
C. Genes linked to increased AMD risk are implicated in drusen formation
D. Genes linked to increased AMD risk are implicated in inflammation

10. A 75-year-old patient with AMD presents to your office for evaluation. On examination you note GA in both eyes. Fundus autofluorescence (FAF) shows focal geographic lesions in both eyes. Which of the following statements is TRUE?

A. The pattern of FAF in this patient puts him at a high risk of GA progression
B. The pattern of FAF in this patient puts him at lower risk of GA progression
C. There is no correlation of progression and pattern of FAF in this patient
D. This patient has a high risk of progression if he has a thick choroid on OCT

11. All of the following statements about the complement system are true, EXCEPT?

A. The complement cascade is a strategic target for GA therapy
B. The complement system is the last line of defense of the immune system
C. The complement system constitutes our innate immunity that does not change as we age
D. The complement system is activated by the adaptive immune system

12. What is the target for the novel GA therapy avacincaptad pegol?

A. C5
B. C3
C. C1q
D. C9

13. According to studies on avacincaptad pegol, which of the following statements is TRUE?

A. After 12 months of treatment, there was a statistically significant decrease in GA progression compared to sham
B. After 12 months of treatment, there was a decrease in GA progression compared to sham, but this was not statistically significant
C. After 12 months of treatment, there was no decrease in GA progression compared to sham
D. After 12 months of treatment, the treatment group progressed to GA at a higher rate than the sham group

14. All of the following statements regarding therapies for GA are TRUE, except?

A. Complement inhibitors are a therapeutic target for GA, as the complement pathway is implicated in the formation of drusen and development of AMD
B. C5 inhibitor eculizumab and tesidolumab failed to show that they could effectively halt or slow the progression of atrophic lesions
C. CFD inhibitor lampalizumab trials showed decreased progression of atrophic lesions in GA
D. Researchers are currently continuing to investigate the complement cascade as a potential target for GA therapy

15. A 68-year-old patient presents for her annual exam. Her VA is 20/20 OU. She notes a bit of decreased contract sensitivity with no other symptoms. She has mild GA in both eyes with a trickling pattern on FAF. She presents to your office 3 years later with complaints of difficulty reading and difficulty performing daily tasks. On FAF, you note significantly worse GA in both eyes, approaching the fovea. She also has 1+ nuclear sclerotic cataracts and mild dry eye. Which of the following is a reasonable treatment option for this patient?

A. Schedule patient for cataract surgery
B. Consider treatment for GA after discussion of risks and benefits
C. Observation without treatment
D. Discussion with patient that no treatment is necessary as her GA will likely not progress further

16. What molecule does the GA therapy ANX007 target?

A. C5
B. C3
C. C1q
D. C9

Before February 17, 2023, optometrists who diagnosed patients with advanced age-related macular degeneration (AMD) knew that one of two possible outcomes existed for their patients upon referral to a retina specialist: either they would be eligible for treatment with any number of intravitreal injections in the event they have neovascular AMD, or they would be monitored but offered no treatment if they were diagnosed with geographic atrophy (GA).

However, pegcetacoplan has now been approved by the FDA for the treatment of GA. The FDA has also completed its filing review and accepted a new drug application for priority review of avacincaptad pegol with a Prescription Drug User Fee Act date of August 19, 2023.

Given how these changes will quickly affect the treatment and referral dynamics of eye care, it is imperative that optometrists improve their understanding of GA's prevalence and burden, as well as perfect their ability to diagnose GA and understand progression patterns common in untreated disease. So, too, must they familiarize themselves with the therapies that may soon be available for their patients.

This supplement, based on a live-virtual symposium that took place prior to the approval of pegcetacoplan, features topics including prevalence, burden, and pathophysiology of GA; detection and progression of GA; latest data from the pipeline; and case presentations and discussions.

—Peter K. Kaiser, MD, Program Chair

GA Prevalence, Burden, and Pathophysiology

MARK T. DUNBAR, OD, FAAO

Optometrists, particularly those who care for older patients, are very familiar with the signs and symptoms of AMD. Drusen and pigmentary abnormalities are anatomic markers that we sometimes see in patients, even those who report no visual disruption. The presence of drusen itself is not an indicator of AMD, as patients with drusen measured 63 µm or less and no pigmentary changes are categorized as having no AMD according to the AMD staging schematic set forth by Ferris et al[1]; this classification is commonly called the Beckman classification system (Figure 1). Patients with drusen from 63 µm to 125 µm and no pigmentary changes have early AMD; patients with at least one drusen larger than 125 µm or any pigmentary change have intermediate AMD.[1] Patients in the early and intermediate stages are commonly characterized as having dry AMD.

Patients have advanced AMD when they demonstrate evidence of a subtype of the disease: wet AMD or GA.[1] GA is diagnosed when at least one sharply demarcated atrophic lesion is observed, and choroidal vessels are visualized through the lesion (Figure 2).[2] Irreversible vision loss occurs following growth of these lesions, particularly when they become centralized.[3]

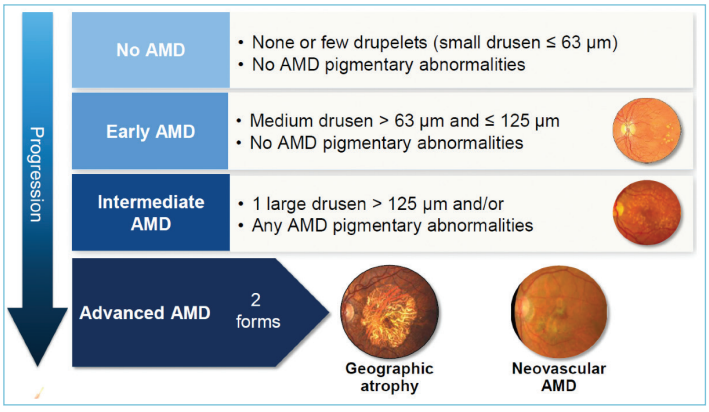


Figure 1. In this visual depiction of the Beckman classification of AMD, dry AMD comprises all nonadvanced forms of AMD. By the time a patient progresses to advanced AMD, they are diagnosed with wet AMD or GA.

In my clinical experience, patients with intermediate AMD should be monitored more closely than those with early AMD. I typically ask patients with intermediate AMD to schedule an examination at least twice a year, and often instruct them to begin nutritional supplementation. Close monitoring in the intermediate AMD window enables prompt intervention in the event of conversion to advanced AMD, and early detection of conversion from intermediate AMD to wet AMD has been a common practice pattern for optometrists. If a therapy for GA is approved by the FDA, we may have to refine our protocols to ensure that we are also detecting conversion from intermediate AMD to GA, thereby facilitating prompt treatment by way of referral.

PREVALENCE AND BURDEN

Global estimates of any-stage AMD place prevalence at 196 million,[4] and forecasts project a worldwide prevalence of 288 mil-

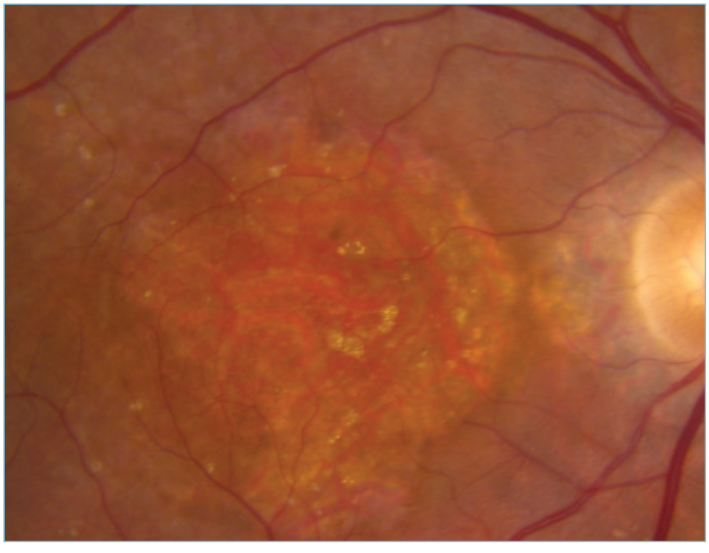


Figure 2. On this color fundus photograph of a retina with GA, underlying choriocapillaris can be seen through a clearly demarcated atrophic lesion.

lion by 2040.[4] Regarding GA in particular, an estimated 3 million patients had GA in the United States in 2020.[5] Given that age is a risk factor for disease, we can expect the prevalence of GA to rise as the population ages. Rudnicka et al found that, among white patients older than 50 years, incidence rates of late-stage AMD quadrupled per decade in age.[6] That same group also estimated that 160,000 new cases per year of GA occurred among white Americans. Non-Hispanic white patients have the highest prevalence of AMD compared to other demographic groups.[7]

Patients with GA have significantly reduced quality of life (QOL) and visual function compared with age-matched control patients.[8] Compared with non-GA peers, patients with GA experience difficulty with reading, exercise, personal hygiene, and domestic chores, and they have significantly more difficulty with near and distance activities, as well as difficulty understanding the limits of activities.[9]

Driving habits are adversely affected by GA. More than half (52%) of patients with GA and a driver's license do not feel comfortable driving during the day[8]; at night, 88% of patients report lack of confidence with driving.[8] An estimated 82% of patients experience worsening year-over-year vision, compared with 25% of control patients ($P < .01$).[8]

Patients with AMD have higher rates of depression than age-matched controls without AMD.[10] Indeed, depression rates may very well be higher among patients with GA than wet AMD: patients with wet AMD who have undergone successful treatment report feeling "cautiously optimistic," whereas those who have GA (and therefore have not received intervention) report feeling "profound loss."[11]

RISK FACTORS AND PATHOPHYSIOLOGY

The current hypothesis for the pathophysiology of GA is that oxidative stress, environmental conditions, and genetic factors contribute to complement deposition between the retinal pigment epithelium and Bruch's membrane.[12,13] Breakdown of the blood-retina barrier, loss of complement regulation, and localized inflammation follow.[12,13] The complement cascade, a branch of the immune system, is implicated in pathophysiology of GA because complement components have been detected in drusen deposits in patients with GA.[12] (*The complement system is discussed in further detail on page 12.*)

Aside from the age- and race-related risk factors discussed above, genetic, physiological, and lifestyle risk factors contribute to a patient's overall risk profile.

Many of genes liked to increased risk of AMD and GA are associated with the immune system. At least two dozen single nucleotide polymorphisms linked to increased risk for AMD have been identified (Figure 3).[14] Genotype has also been implicated in drusen formation and inflammation.[15]

Physiological risk factors for AMD development include high body mass index,[14] dyslipidemias (ie, high total cholesterol and low-density lipoproteins, low high-density lipoproteins),[16] and chronic herpes simplex B infection.[17] Use of some diabetes medications and anticholinergic medications are linked with increased risk of AMD.[18,19] Patients with a history of cardiovascular disease,[14,18] diabetes,[18] and other ocular conditions[18] such as glaucoma, cataract, and retinal disorder are at higher risk for AMD.

Common Variants		
CFH – Y402H	*LIPC*	*TNFRSF10A*
CFH – rs1410996	*CETP*	*IER3/DDR1*
CFB	*ABCA1*	*SLC16A8*
C2	*TIMP3/SYN3*	*RAD51B*
C3	*VEGFA*	*ADAMTS9*
CFI	*COL10A1*	*B3GALTL*
ARMS2/HTRA1	*COL8A1*	*TGFBR1*
Rare Variants		
CFH – R1210C	*C3* – K155Q	*C9* – P167S

CFI- increased burden of disease with multiple variants.

Figure 3. Single nucleotide polymorphisms associated with the development of AMD are listed here. ARMS2 and the CFH variant Y402H are among those often discussed by clinicians and researchers. Adapted from: Sobrin L, Seddon JM. Nature and nurture- genes and environment-predict onset and progression of macular degeneration. *Prog Retin Eye Res.* 2014;40:1-15.

Lifestyle and environmental dynamics also affect risk for AMD development. Smoking is among the most important lifestyle factor. Nearly 30% of AMD cases in women may be partially attributable to smoking,[14] and models predicting vision loss secondary to AMD or GA use smoking as a factor for calculating risk.[20] Diets with low levels of antioxidants, vitamins, and minerals,[14] as well as diets that are high in saturated fats and dietary cholesterol,[21] are linked with increased risk of AMD. Elevated exposure to sunlight[14,22] and high levels of alcohol consumption[23] are also linked with elevated AMD risk.

ASSESSING VISION IN PATIENTS WITH GA

BCVA is an unreliable metric of vision loss due to GA. The foveal-sparing nature of some disease may still allow some patients to read lines on an eye chart despite an overall decline in visual function.[24] Low-luminance visual acuity (LLVA), low-luminance deficit (LLD), reading speed assessment, and microperimetry, may all be more useful mean so measuring vision function in patients with GA.

GA patients experience significant impairment in dimly lit environments. After assessing LLVA, optometrists can determine LLD by calculating the difference between LLVA and conventional BCVA.[24] LLVA is a strong predictor is vision loss in patients with GA.[24] Use of reading speed assessments, which require a patient to look at more than just a single letter typically shown on an eye chart, may better quantify loss of visual function in some patients.[25] Microperimetry testing, during which patients push a

button to acknowledge that they perceive light stimulus on their retina, may help identify areas of scotoma. Results from microperimetry tests can be overlayed atop fundus photographs,[26] allowing clinicians to compare structure and function.

To view this article's references, log in to your Evolve account and scan the QR code on page 3.

Imaging GA and Tracking Disease Progression

PRIYA SHARMA VAKHARIA, MD

As we approach an era of therapeutic possibility for patients with geographic atrophy (GA), characterizing disease may be key to identifying which patients may have GA, whether they are eligible for intervention, and how their disease has responded to therapy. By leveraging the power of imaging tools, optometrists can provide a detailed analysis of a patient's anatomy upon referral to a retina specialist, thereby optimizing the patient experience via clear communication.

Multiple imaging modalities have been used to characterize GA. Among them are flash color fundus photography (CFP), short-wave fundus autofluorescence (FAF), near infrared reflectance (NIR), confocal/multicolor imaging, and OCT. A detailed list of their respective advantages and disadvantages can be found in Figure 1.

FLASH COLOR FUNDUS PHOTOGRAPHY

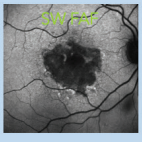
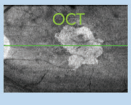
CFP has been a standard imaging technique for determining presence of GA for decades. Sharply demarcated borders, depigmentation, and increased visibility of choroidal vessels on CFP is one of the standard definitions for GA.[1,2] Use of CFP may be popular in part because of its relative ubiquity in optometric and ophthalmic clinics. Interpretation of CFP may be intuitive for some clinicians, as the image produced by this method closely mirrors what we see upon fundoscopic examination. Still, experienced image interpreters may be needed from time to time.

In some instances, use of CFP is sufficient for diagnosing GA, as areas of depigmentation are clearly defined and visibility of choroidal vessels is obvious (Figure 2A). In other instances, however, CFP insufficiently contrasts areas of atrophy and otherwise healthy tissue (Figure 2B). CFP may not be a good tool for quantifying lesion area, in part due to the fact that lesion borders may be inadequately depicted. Confocal/multicolor fundus photographs provide improved color contrast, but have not yet been validated as a tool for measuring GA lesions, and the technology is not widely available in clinics.

SHORT-WAVE FUNDUS AUTOFLUORESCENCE

FAF has been used as a primary endpoint measure in many of the clinical trials evaluating potential therapies for GA.[3,4] Indeed, it has been called the "gold standard for evaluating progressive GA enlargement."[5] It may be a useful modality to depict disease in patients whose CFP results in unsatisfactorily depicted GA lesion borders, or in patients whose clinicians wish to track measurable lesion areas over time (Figure 2C). Still, FAF is uncomfortable for patients and is not as widely available at CFP and OCT, making it impractical in some clinical settings.

Clinicians aiming to estimate the risk of progression in patients with GA may rely on FAF. Larger lesions as shown on FAF progress faster than smaller lesions, and multifocal lesion patterns

IMAGING TECHNOLOGY	ADVANTAGES	DISADVANTAGES
	• Historical standard • Closest correlate to biomicroscopy • Visualizes broad range of fundus abnormalities • Robust to image hemorrhages and pigmentary changes	• Reduced contrast • Limited reliability • Strongly affected by optical media • Patient discomfort • Experienced examiner required
	• High contrast • Regulatory acceptance • Extensive experience • Already used for primary endpoint measurement • Strongly decreased signal correlates with loss of function • Allows for refined phenotyping	• Sensitive to nuclear lens opacities and vitreous floaters • Assessment of foveal region difficult • Semi-automated atrophy quantification may be hindered in certain conditions • Patient discomfort
	• Resistant to media opacities • Auxiliary for foveal assessment • Enables detection of reticular pseudodrusen and atrophy • Build-in in most OCT	• Lack of validation studies for late-stage AMD • Findings are of yet unstudied specificity • Cannot be used as stand-alone technology
	• High precision and contrast • Displays many, but not all findings from CFP • Hyper-pigmentation difficult to distinguish from hemorrhage • Contrast between atrophy and fibrosis • Detection of pseudodrusen	• No true-color image • Mainly carrying the information from NIR • Limited evidence from validation studies • Limited availability
	• Broadly available • Cross-sectional morphology of retina, RPE, and choroid • Correlated with histology • Validated to assess RPE atrophy progression and neovascular changes • Anatomical tracking functions for exact repositioning of follow-up scans • Advances in lateral resolution and scanning speed expected in near future • Identification of pre-atrophic features • Comfortable for patients	• Scan field limited • Interpretation strongly dependent on imaging quality • Lack of industry standards • 3D datasets require sophisticated analysis software and longer reading times for detailed slab analyses of retinal and choroidal layers • Automated segmentation imperfect and instrument dependent • Definition of atrophy border and relevance of certain prognostic biomarkers still controversial

NIR = near infrared reflectance; SW FAF = short wave fundus autofluorescence
CFP = color fundus photography; NIR = near infrared reflectance; RPE = retinal pigment epithelium

Figure 1. The advantages and disadvantages of CFP, FAF, NIR, confocal/multicolor imaging, and OCT are listed here. In general, CFP, OCT, and NIR imaging will be the most accessible, while FAF and confocal/multicolor imaging provide the highest contrast.

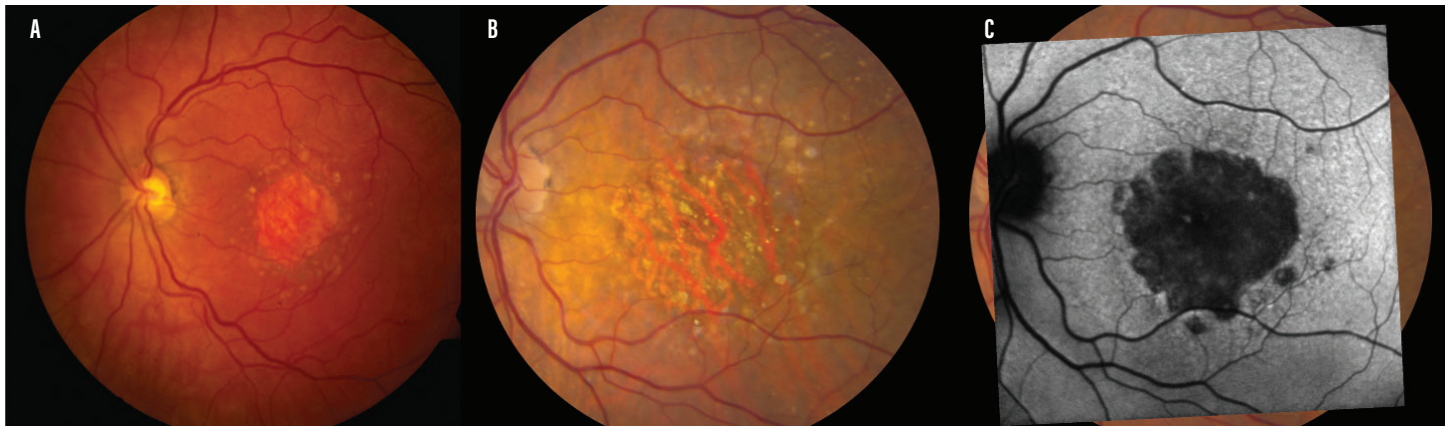


Figure 2. In some cases, CFP clearly shows an area of defined depigmentation and increased visibility of choroidal vessels (A). In other cases, CFP is not as useful. Sometimes, even when it clearly depicts atypical retinal tissue, it is difficult to determine where atrophy starts and stops (B). Clinicians seeking to quantify lesion area or to better depict the area of atrophy in such a patient may need to turn to another imaging modality, such as FAF. An overlay of an FAF image atop the CFP image from Figure 2B illustrates how FAF can be used to show clear areas of atrophic tissue (C).

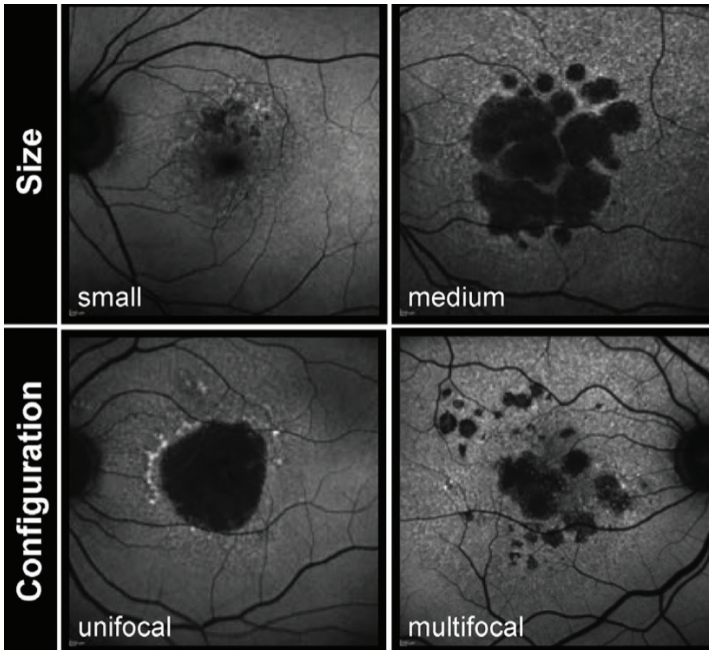


Figure 3. Lesion size and configuration as depicted on FAF can help clinicians estimate the risk of GA lesion progression. Lesions in the left column (small and unifocal) progress slower than lesions in the right column (larger and multifocal). This may be due to the larger total perimeter of larger and multifocal lesions.

progress faster than unifocal lesion patterns (Figure 3).[6] This may be due to the larger total perimeter of larger and multifocal lesions compared with smaller and unifocal lesions.

Fleckenstein et al described a series of diffuse patterns on FAF, which are "characterized by levels of abnormal increased FAF intensities extending beyond the border zone" of GA lesions,[7] and Bindewald described other patterns that included banded lesions, which comprise lesions with increased autofluorescence encircling the entire GA lesion (Figure 4).[8] Banded and diffuse lesions are more likely to progress than other lesion subtypes.[8]

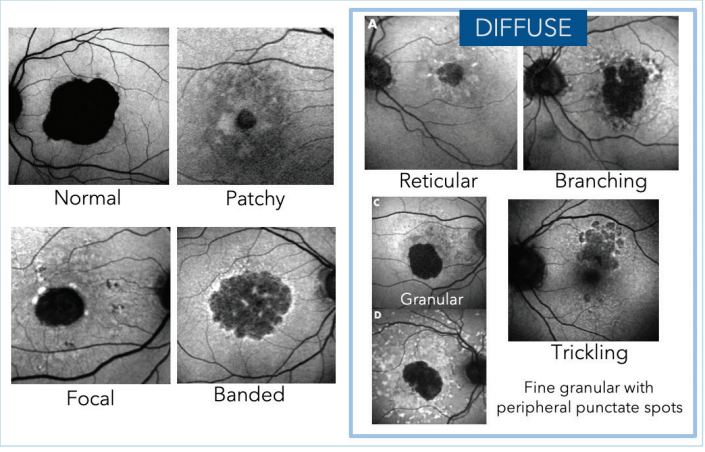


Figure 4. Banded and diffuse patterns as depicted on FAF are linked with higher risk of disease progression compared with lesions categorized as normal, patchy, or focal.

OPTICAL COHERENCE TOMOGRAPHY

Use of OCT imaging allows clinicians to examine a cross-section of retinal tissue in a fast, noninvasive manner and on a modality that is commonly accessible in modern clinics. OCT's depiction of the separation between the retinal pigment epithelium (RPE) and Bruch's membrane may be useful to eye care providers investigating potential GA. Thin choroid and junctional zone abnormalities as depicted on OCT are linked with higher risk of progression.[9]

The Classification of Atrophy Meeting (CAM) group sought to outline criteria for evaluating GA and pre-GA conditions in patients on OCT imaging.[10] Among the group's consensus findings were definitions for two conditions: incomplete RPE and outer retinal atrophy (iRORA) and complete RPE and outer retinal atrophy (cRORA; Figure 5). Patients with cRORA, the most advanced atrophic condition per the CAM group, must meet four OCT criteria[10]:

- Region of hypertransmission at least 250 µm in diameter
- RPE zone of attenuation/disruption at least 250 µm in diameter

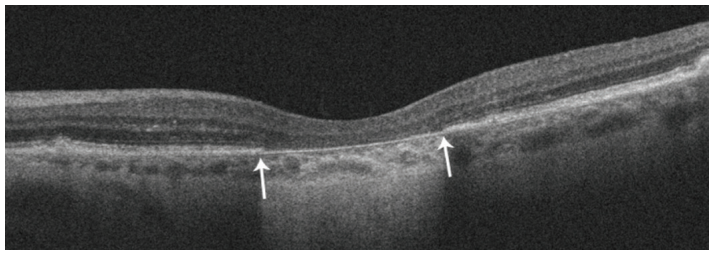


Figure 5. In this OCT image, all four criteria of cRORA have been satisfied: the area of hypertransmission is at least 250 µm, the zone of attenuation of the RPE is at least 250 µm, overlying photoreceptor degeneration is present, and no scrolled RPE (or other signs of RPE tear) are observed.

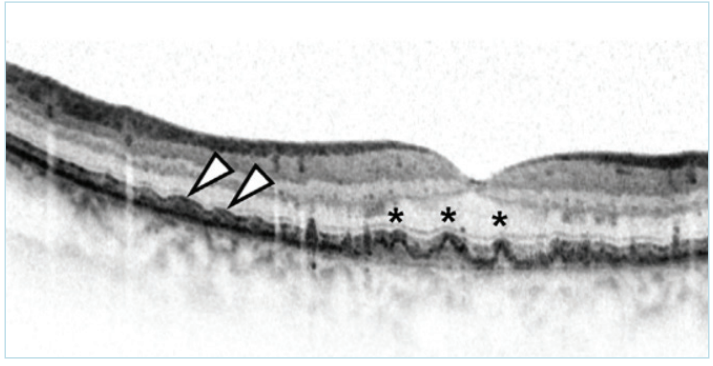


Figure 6. RPD (at arrows) as depicted on OCT imaging. The presence of RPD is associated with rapid progression of GA. The asterisks denote soft drusen.

- Evidence of overlying photoreceptor degeneration
- Absence of scrolled RPE or other signs of an RPE tear

Use of the CAM group's nomenclature may yield more precise characterization when diagnosing retinal atrophy. Further, clinicians who use OCT to evaluate GA in a busy clinic may find OCT to be convenient and efficient, and that the CAM group's guidance facilitates image interpretation.

NIR, a feature commonly built into many OCT platforms, has yet to be validated as a standalone imaging modality for GA evaluation. Still, some clinicians choose to pair it with OCT imaging when probing for the presence of reticular pseudodrusen (RPD), also called subretinal drusenoid deposits. RPD appear below the retina and atop the RPE (Figure 6), and have been associated with elevated risk of rapid GA progression.[11]

CONCLUSION

For a long time, eye care providers who diagnosed patients with GA may have felt as though tracking disease progression was a futile task: without an available treatment, observing the rate or shape of anatomic disruption was of little use to a patient being robbed of their vision. As we approach an era of possible treatments, primary eye care providers who send imaging reports to retina specialists upon referral for GA evaluation will ensure that collaboration is maximized and patient history is effectively communicated.

To view this article's references, log in to your Evolve account and scan the QR code on page 3.

Pipeline Therapies for GA: Understanding the Complement System and a Look to the Future

PETER K. KAISER, MD

Two pipeline therapies have been submitted to the FDA for the treatment of geographic atrophy (GA): pegcetacoplan and avacincaptad pegol.[1,2] Both of these potential therapies, as well as a handful of other interventions under investigation, target the complement system. Because a clinician's familiarity with the complement system is foundational to understanding how their patient will fit into the larger treatment landscape, it behooves us to explore it here.

AN INTRODUCTION TO THE COMPLEMENT SYSTEM

The complement system is part of the innate immune system, and its primary role is to protect the body from foreign pathogens. The complement system's cascade of events is activated by one of three pathways: the classical pathway, the lectin pathway, and the alternative pathway (Figure 1). The complement cascade terminates with the formation of membrane attack complex (MAC), resulting in cell death.[3]

The classical pathway is activated mainly by an antigen-antibody complex, but is also activated by c-reactive protein and amyloid beta. C1q is one of the complement components activated at the start of the classical pathway, which in turn activates C3 convertase.[3] C3 convertase is responsible for cleaving C3 into components C3a and C3b. Next, C3b activates C5 convertase, which cleaves C5 into C5a and C5b, the latter of which joins C6, C7, C8, and C9 to form MAC.[4] MAC opens a pore on in foreign cell's surface, thereby destroying the cell.

The lectin pathway is activated in part by mannose-binding lectin-associated serine proteases (MASPs).[5,6] Initiation of the lectin pathway also results in the cleavage of C3, and the downstream effects thereafter are identical to those described in the classical pathway section.

The majority of complement activation is through the alternative pathway. The alternative pathway is spontaneously activated, resulting in auto-hydrolysis of C3 and the associated downstream activities.[7] Given that the alternative pathway is activated spontaneously, it may be of particular interest to patients with GA. The rate-limiting step is the presence of complement factor D (CFD), and the alternative pathway effectively amplifies the activity of the classical and lectin pathways.[8]

Drusen are a hallmark clinical feature of age-related macular degeneration (AMD), and are used to classify AMD stage as outlined in the aticle authored by Mark T. Dunbar, OD, FAAO.[9] Exploration of drusen in patients with GA has shown that C1q, C3, C5, and C3b, C6, C7, C8, and C9 are present in drusen, implicating the complement

CASE STUDIES

Case No. 1: GA Progression Over Time on Fundus Autofluorescence

By Priya Sharma Vakharia, MD

A patient presented for her regular eye evaluation reporting no visual disruption. Upon examination on fundus autofluorescence (FAF), evidence of bilateral geographic atrophy (GA) was observed (Figure 1). Specifically, this patient had an extrafoveal lesion in her right eye and a multifocal extrafoveal lesion in her left eye.

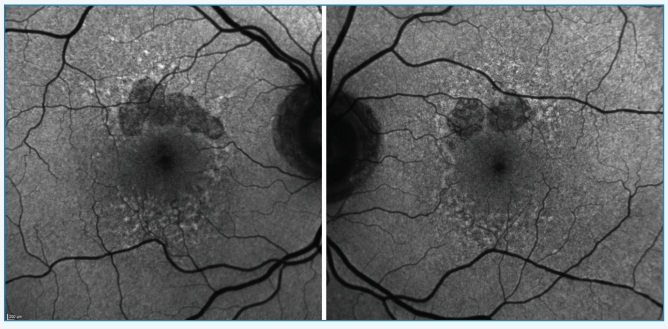


Figure 1. A patient presents with bilateral evidence of GA. Her VA measured 20/20 in both eyes, and she reported no visual disruption.

The patient returned 3 years later reporting difficulty reading. Examination on FAF showed that her GA lesion area had increased, with foveal encroachment (Figure 2). The patient's VA was 20/20 in her right eye and 20/25 in her left eye. The disconnect between her measured visual acuity and her visual function speaks to the extrafoveal nature of her disease, and points to why tests other than BCVA have utility in assessing the visual function of GA patients.

Six months later, the patient returned (Figure 3). Reading difficulty remained, and VA had decreased to 20/30 in both eyes. Lesions in each of her eyes had grown.

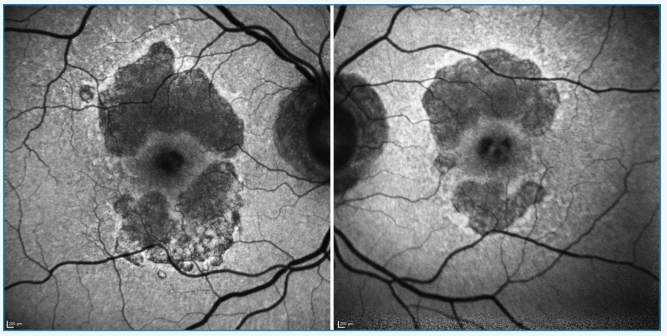


Figure 2. Three years after initial presentation, the patient's VA is 20/20 OD and 20/25 OS. She reported difficulty reading.

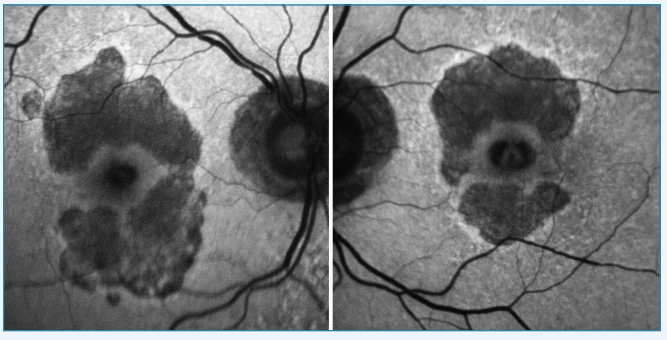


Figure 3. The patient returned 6 months later (3.5 total years after initial presentation). VA measured 20/30 in both eyes, and the patient still had difficulty reading. Encroachment upon the foveal center will likely occur next.

Questions remain about when intervention is best for a patient like this. Convincing a patient to receive regular intravitreal injections when her vision is 20/20 may be difficult. FAF may be a useful tool when educating a patient such as this, as lesion area can clearly be identified. Regardless of when intervention is initiated, prompt referral to a retina specialist upon detection of GA lesions will be an important element of placing this patient into a treatment protocol. If an optometrist has images such as those in Figure 1 or other relevant elements of patient history to send along with referral, then the patient experience will be optimized.

CASE STUDIES

Case No. 2:
Depiction of GA Progression on OCT During a 6-Year Period

By Mark T. Dunbar, OD, FAAO

In 2015, an 80-year-old man presented for an eye examination complaining of reduced vision. Suspecting that the patient may have had neovascular age-related macular degeneration, OCT imaging was performed (Figure 1). No evidence of macular edema or fluid was observed. However, evidence of hypertransmission and retinal pigment epithelium (RPE) zone of attenuation were present.

The patient was observed during a 6-year period, by the end of which VA had dropped to 20/100 in his right eye and 20/50 in his left eye (Figure 2). Based on OCT imaging, this patient has complete retinal pigment epithelium and outer retinal atrophy (cRORA). His OCT images meet the four criteria for such a diagnosis: a region of hypertransmission at least 250 µm in diameter, an RPE zone of attenuation at least 250 µm in diameter, evidence of overlying photoreceptor degeneration, and the absence of scrolled RPE or other signs of an RPE tear.

Before the era of GA therapies–if, indeed, we are to arrive there soon–nothing could be done for this patient: his disease had advanced unchecked and robbed him of his vision. We cannot know if this patient would see value in submitting to regular intravitreal injections for his right eye, but he may wish to preserve vision in his left eye. Referral to a retina specialist for this patient should include these OCT images, as they clearly characterize the scope of this patient's GA progression.

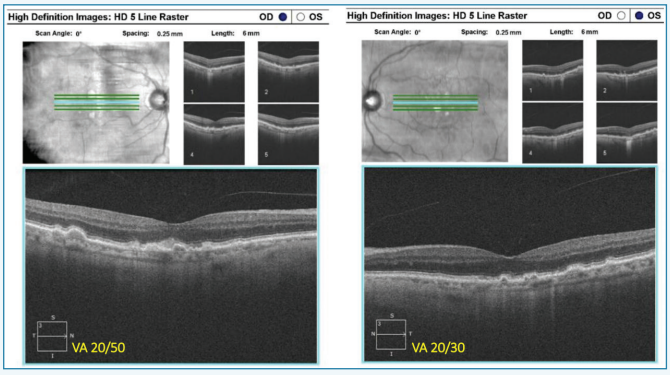


Figure 1. A patient presented to the clinic with reduced vision. Evidence of hypertransmission and an RPE zone of attenuation is present upon examination with OCT. The patient presented in 2015, when potential therapies for GA were nearly a decade from FDA submission.

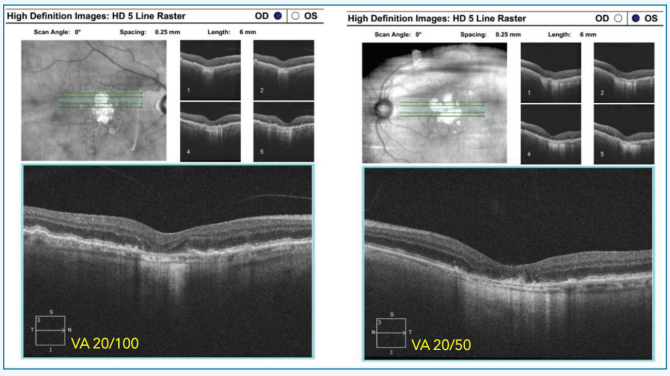


Figure 2. Six years later, the patient returned to the clinic. VA dropped from 20/50 to 20/100 in his right eye, and from 20/30 to 20/50 in his left eye. At this point, the patient's GA should also be considered cRORA.

system in the pathogenesis of GA.[10] Moreover, genome-wide association studies have implicated mutations in the complement cascade as important risk factors for developing AMD.[11]

A LOOK AT THE PIPELINE

A handful of complement inhibitors for the treatment of GA failed to show that they could safety and effectively halt or slow the progression of atrophic lesions. Among them are the C5 inhibitors eculizumab[12] and tesidolumab[13] and the CFD inhibitor lampalizumab.[14] Despite the inability of these drugs to affect the progression of GA, researchers continued to investigate the complement cascade as a potential target for GA therapy and have made significant progress. A review of some potential therapies targeting the complement system follows.

Complement Inhibition: Phase 3 Studies

Avacincaptad pegol is a C5 inhibitor that is delivered by intravitreal injection. Researchers in the pivotal GATHER1 and GATHER2 studies evaluated the safety and efficacy of avacincaptad pegol compared with sham for the treatment of GA. In the

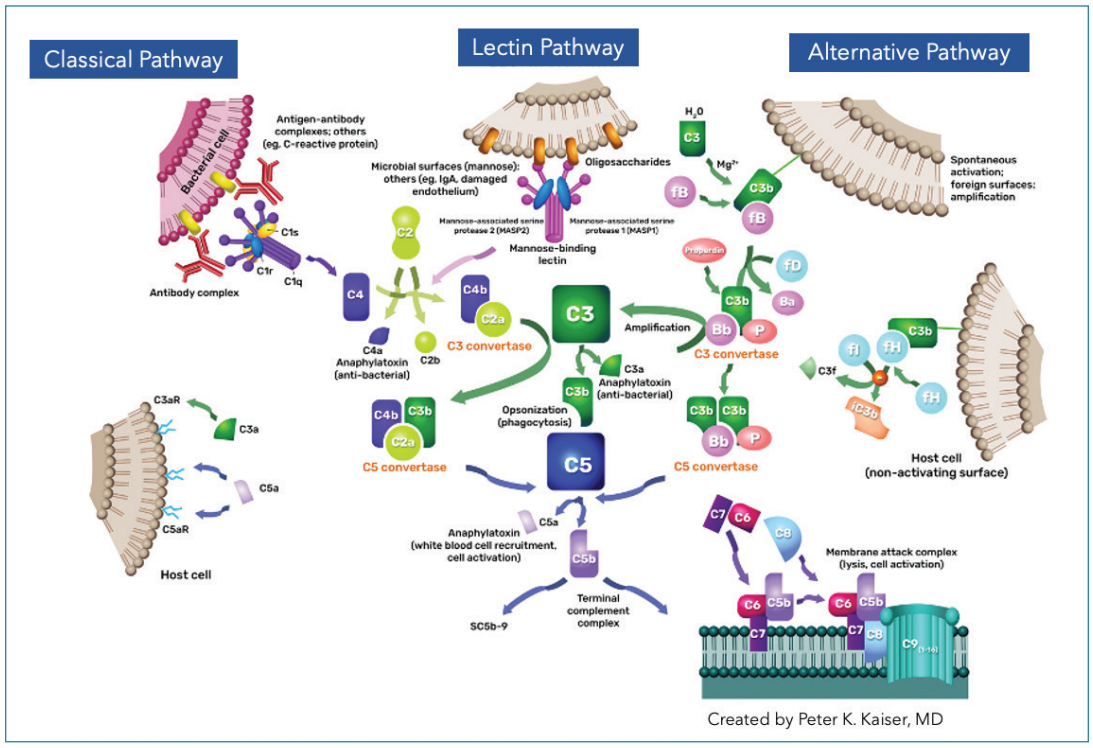


Figure 1. The complement system is activated by one of three pathways, termed classical, lectin, and alternative. All three pathways converge at C3; pegcetacoplan targets C3. Further downstream, avacincaptad pegol targets C5. The complement system terminates at the formation of MAC, which results in cell lysis.

phase 2b/3 GATHER1 study, patients were randomly assigned to receive monthly avacincaptad pegol (at either a 2-mg or 4-mg dose) or sham[15]; in the phase 3 GATHER2 study, patients received monthly avacincaptad pegol or sham, and those in the avacincaptad pegol arm were re-assigned to monthly or every-other-month (EOM) after month 12.[16]

Figure 2 shows efficacy results from GATHER1 and GATHER2. In GATHER1, treatment with avacincaptad pegol 2 mg or avacincaptad pegol 4 mg resulted in a reduction in the mean growth rate of GA of 0.292 mm and 0.312 mm, respectively.[15] Both rates were statistically significant compared with sham. In GATHER2, the mean rate of GA lesion area as measured by square root transformation (slope) was 0.336 mm in the treatment arm compared with 0.392 mm in the sham arm (difference 0.056 mm, or 14.3%).[16] This difference, too, was statistically significant.

The safety profiles in GATHER1 and GATHER2 were favorable, with only a single instance of intraocular inflammation (IOI) detected, which was transient and mild.[16] Approximately 4.1% of sham patients developed choroidal neovascularization compared with approximately 6.7% in the avacincaptad pegol 2 mg arms, with 4.9% being exudative.[16]

Pegcetacoplan is a C3 inhibitor that is delivered via intravitreal injection. The safety and efficacy of pegcetacoplan for the treatment of GA was assessed in the phase 3 DERBY and OAKS studies.[17] Patients were randomly assigned to receive pegcetacoplan monthly or EOM, or sham monthly or EOM.

At 12 months, patients in OAKS demonstrated a statistically significant reduction in GA lesion growth in the monthly and EOM arms compared with pooled sham.[17] In DERBY, however, statistical significance was not achieved in either treatment arm compared with pooled sham.[17] A prespecified analysis of the combined treatment arms found that monthly and EOM treatment significantly reduced the rate of GA lesions growth compared with pooled sham.[17]

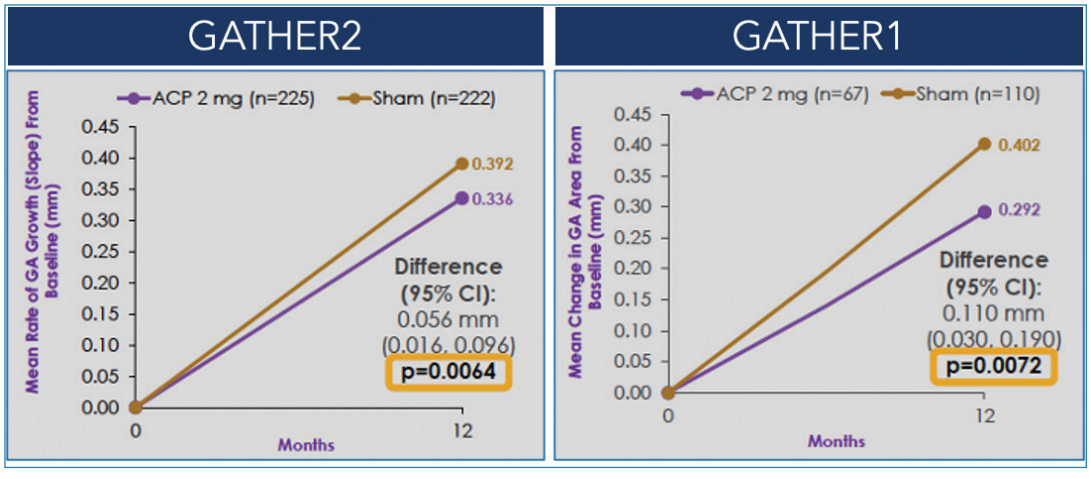


Figure 2. Results from the GATHER1 and GATHER2 pivotal studies show that avacincaptad pegol 2 mg significantly slowed the rate of GA lesion growth compared with sham.

Researchers continued to investigate the effects the drug had on GA lesion growth. At month 18, it was found that pooled monthly and EOM arms, respectively, demonstrated reductions in GA lesion growth of 20% and 17% compared with sham.[18] Reduction rates of pooled monthly and EOM, respectively, were 30% and 24% at 24 months.[19] The

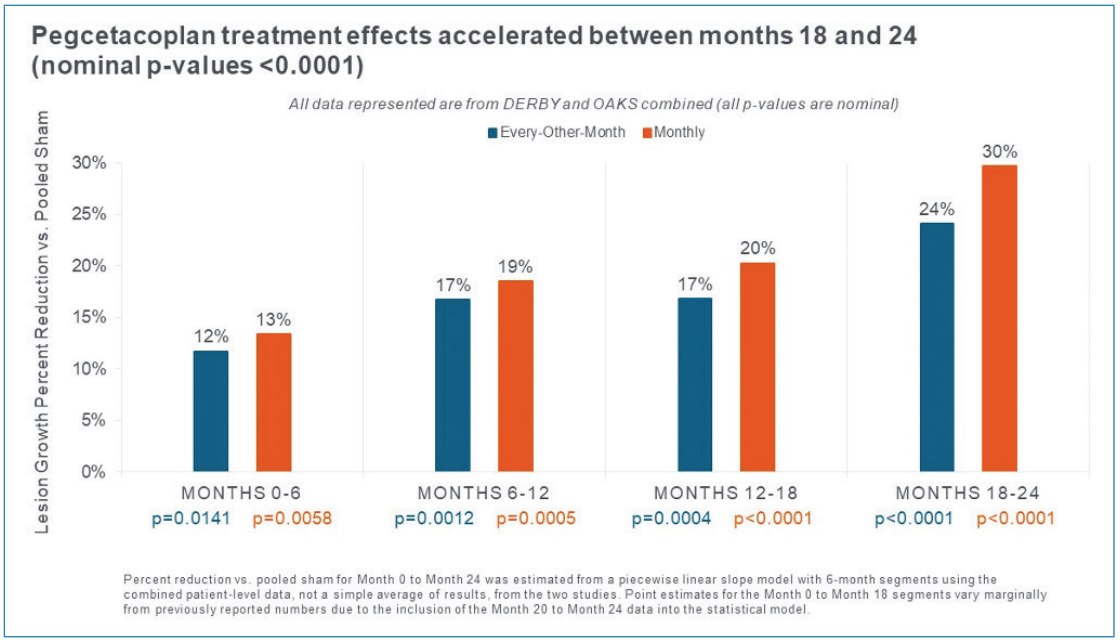


Figure 3. At months 18 and 24, treatment effect of monthly pegcetacoplan had accelerated compared with month 12. The treatment effect of EOM pegcetacoplan compared with sham was highest at month 24.

differences at months 18 and 24 were statistically significant when using nominal *P* values (Figure 3). These data have been added pegcetacoplan's regulatory filing with the FDA.

Safety data from the 12-month timepoint showed that new-onset rates of exudative CNV were 6.0%, 4.1%, and 2.4% in the pooled monthly, EOM, and sham arms. IOI rate per patient was 1.1% per injection when excluding four cases linked to drug impurity from 2018.[17]

We should note that in the pivotal studies for both avacincaptad and pegcetacoplan, longer treatment resulted in a greater delta compared with sham. This may be a key educational point that eye care providers are tasked with communicating to patients—that is, that the treatment effect of these drugs may be more important as time goes on.

Complement Inhibition: Early Phase Studies

The C1q inhibitor ANX007 is under investigation in the phase 2 ARCHER study.[20] It is delivered via intravitreal injection. Data from a phase 1b study showed that ANX007 was well tolerated and complete suppression of C1q was achieved at 4 weeks at the two highest dose levels.[20]

The drug GT005 is a gene therapy under investigation for producing recombinant complement factor I (CFI). CFI is necessary to reduce the overactivity of the alternative pathway. It is under investigation in the phase 2 HORIZON and EXPLORE studies, during which GT005 will be dosed via transvitreal or Orbit SDS subretinal injection.[21,22] In a phase 1/2 study, patients with GA who received one of three different doses of GT005 had sustained levels of vitreous CFI 7 to 24 months after treatment.[23]

Stem Cell Therapy

Stem cell therapy may one day have applications in GA treatment. A phase 1/2a study evaluating the safety and efficacy of a human embryonic stem cell–derived retinal pigment epithelium patch is underway.[24] Mild and moderate subretinal hemorrhages and macular have been reported following grafting of this patch,[25] and studies in stem cell–derived therapies are ongoing.[25]

Patients sometimes visit eye care clinics inquiring about stem cell therapies, aware of their promise in treating other diseases. These patients should be advised that, although small studies have been initiated, there is no stem cell–based therapy for AMD or GA approved by the FDA. Further, patients should be educated that clinics offering cell therapy for AMD or GA are predatory, and that vision loss and other adverse events have been reported following such unapproved treatments.[26]

CONCLUSION

We may soon be entering a new era of GA therapy. If we do, optometrists can expect to field questions from patients about the referral process and about therapies. And although conversations with patients are oftentimes best kept to a high-concept level, knowledge about the overall treatment and pipeline landscape will be key to the gatekeepers of eye care having intelligent, thoughtful conversations with patients about the value of adherence to therapy. ■

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CONTEMPORARY MANAGEMENT OF GEOGRAPHIC ATROPHY: EVOLVING APPROACHES TO DIAGNOSIS, CHARACTERIZATION, AND THERAPY

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COPE Expiration Date: February 29, 2024

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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 educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
____ >50

Region
___ Midwest
___ Northeast
___ Northwest
___ Southeast
___ Southwest

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Summarize the prevalence of age-related macular degeneration and GA and define the burden of illness linked specifically to GA	_____	_____	_____
Comprehend and **explain** the pathogenesis of GA	_____	_____	_____
Describe GA disease detection and factors influencing progression	_____	_____	_____
Appraise the therapies targeting GA that have previously been explored	_____	_____	_____
Articulate the most important data related to drug candidates in the pipeline, with a special emphasis on those candidates furthest along in development	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to comprehend and explain the pathogenesis of geographic atrophy (GA) (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. All of the following are Classification of Atrophy Meetings (CAM) criteria for diagnosing complete retinal pigment epithelial (RPE) and outer retinal atrophy EXCEPT?

A. Region of hypertransmission ≥ 250 µm in diameter
B. RPE zone of attenuation/disruption ≤250 µm in diameter
C. Evidence of overlying photoreceptor degeneration
D. Absence of scrolled RPE or other signs of an RPE tear

3. A 65-year-old woman presents to your office for routine eye exam. On exam, you note a few drusen >125 mm in her right eye, with pigmentary abnormalities in her left eye. What stage age-related macular degeneration (AMD) does she have?

A. Early AMD
B. Intermediate AMD
C. Severe AMD
D. Advanced AMD

4. Your 78-year-old patient with AMD presents for follow-up. You note bilateral large drusen >125 mm on exam primarily in the fovea. On fundus autofluorescence, you note these lesions have a banded GA lesion border pattern. You also note the presence of reticular pseudodrusen. All of the following are risk factors for progression of AMD in this patient, EXCEPT?

A. Larger baseline lesions size
B. Foveal lesion location
C. Presence of reticular pseudodrusen
D. Banded/diffuse GA lesion border patterns

5. All of the following are suitable tests to assess GA progression, EXCEPT:

A. Contrast sensitivity measurement
B. Dark adaptation
C. Reading speed
D. Best corrected visual acuity

6. A 75-year-old patient presents to your office for evaluation. You note bilateral AMD pigmentary abnormalities, but an otherwise normal exam. What stage of AMD does this patient have?

A. No AMD
B. Early AMD
C. Intermediate AMD
D. Advanced AMD

7. What is the approximate prevalence of people worldwide affected by late-stage dry AMD (GA)?

A. ~ 2 million
B. ~ 5 million
C. ~ 7 million
D. ~ 10 million

8. What is the greatest risk factor for AMD?

A. Aging
B. Diet high in saturated fat
C. History of excessive sun exposure
D. Male sex

9. All of the following statements about the genetic risks for AMD are true, EXCEPT?

A. The key genes linked to AMD/GA involve the immune/complement systems
B. Genes linked to increased AMD risk are implicated in decrease of reactive oxygen species
C. Genes linked to increased AMD risk are implicated in drusen formation
D. Genes linked to increased AMD risk are implicated in inflammation

10. A 75-year-old patient with AMD presents to your office for evaluation. On examination you note GA in both eyes. Fundus autofluorescence (FAF) shows focal geographic lesions in both eyes. Which of the following statements is TRUE?

A. The pattern of FAF in this patient puts him at a high risk of GA progression
B. The pattern of FAF in this patient puts him at lower risk of GA progression
C. There is no correlation of progression and pattern of FAF in this patient
D. This patient has a high risk of progression if he has a thick choroid on OCT

11. All of the following statements about the complement system are true, EXCEPT?

A. The complement cascade is a strategic target for GA therapy
B. The complement system is the last line of defense of the immune system
C. The complement system constitutes our innate immunity that does not change as we age
D. The complement system is activated by the adaptive immune system

12. What is the target for the novel GA therapy avacincaptad pegol?

A. C5
B. C3
C. C1q
D. C9

13. According to studies on avacincaptad pegol, which of the following statements is TRUE?

A. After 12 months of treatment, there was a statistically significant decrease in GA progression compared to sham
B. After 12 months of treatment, there was a decrease in GA progression compared to sham, but this was not statistically significant
C. After 12 months of treatment, there was no decrease in GA progression compared to sham
D. After 12 months of treatment, the treatment group progressed to GA at a higher rate than the sham group

14. All of the following statements regarding therapies for GA are TRUE, except?

A. Complement inhibitors are a therapeutic target for GA, as the complement pathway is implicated in the formation of drusen and development of AMD
B. C5 inhibitor eculizumab and tesidolumab failed to show that they could effectively halt or slow the progression of atrophic lesions
C. CFD inhibitor lampalizumab trials showed decreased progression of atrophic lesions in GA
D. Researchers are currently continuing to investigate the complement cascade as a potential target for GA therapy

15. A 68-year-old patient presents for her annual exam. Her VA is 20/20 OU. She notes a bit of decreased contract sensitivity with no other symptoms. She has mild GA in both eyes with a trickling pattern on FAF. She presents to your office 3 years later with complaints of difficulty reading and difficulty performing daily tasks. On FAF, you note significantly worse GA in both eyes, approaching the fovea. She also has 1+ nuclear sclerotic cataracts and mild dry eye. Which of the following is a reasonable treatment option for this patient?

A. Schedule patient for cataract surgery
B. Consider treatment for GA after discussion of risks and benefits
C. Observation without treatment
D. Discussion with patient that no treatment is necessary as her GA will likely not progress further

16. What molecule does the GA therapy ANX007 target?

A. C5
B. C3
C. C1q
D. C9

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this 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
You would 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 activity; may we contact you by email in 3 months to inquire if you have made changes to your practice based on this activity? If so, please provide your email address below.

_____

_____