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Retina Today

GEOGRAPHIC ATROPHY: INSIGHTS INTO CURRENT MANAGEMENT AND POTENTIAL THERAPIES

A CME activity provided by Evolve Medical Education LLC.

This activity is supported by an unrestricted educational grant from Apellis Pharmaceuticals.

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Geographic Atrophy:

Insights Into Current Management and Potential Therapies

Release Date: January 18, 2021

Expiration Date: February 28, 2022

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This continuing medical education (CME) activity captures content from a webinar series.

ACTIVITY DESCRIPTION

This supplement focuses on the management of patients with geographic atrophy (GA). The faculty reviews the prevalence of GA, risk factors for disease, ideal imaging modalities to diagnose and monitor its progression, and the growing pipeline of GA treatments and their mechanisms of action.

TARGET AUDIENCE

This certified CME activity is designed for retina specialists, ophthalmologists, and other professionals involved in the treatment and management of patients GA.

LEARNING OBJECTIVES

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

- **Describe** the prevalence of age-related macular degeneration (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 for CME Credit.

1. Please rate your confidence in your ability to evaluate the functional and anatomic outcomes used in managing patients with 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. GA accounts for what percentage of legal blindness in North America?

- a) 5%
- b) 10%
- c) 20%
- d) 33%

3. What is the most important risk factor for developing GA?

- a) Smoking
- b) Increasing age
- c) Family history
- d) Female gender

4. 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.

5. The lectin, classical, and alternative complement pathways all converge on what molecule?

- a) Complement Factor H
- b) Complement Factor 3
- c) Complement Factor 5
- d) Membrane attack complex

6. All of the following are risk factors for faster GA lesion size growth EXCEPT:

- a) Larger lesions
- b) Multifocal lesions
- c) Presence of reticular pseudodrusen
- d) Focal hyperautofluorescence at edge of lesion

Clinical Evaluation of Geographic Atrophy

Knowing how to assess, image, and classify patients with GA will be key to determining if future therapies are effective.

ALEKSANDRA RACHITSKAYA, MD

In the literature, wet and dry age-related macular degeneration (AMD) has been associated with decreased mobility and driving ability.¹ Patients with advanced dry AMD, also called geographic atrophy (GA), also might report reduced ability to read, social isolation, and inability to maintain personal hygiene. Patients note diminished confidence with commonplace tasks they performed before disease progression. For example, among patients with GA who have a driver's license, 50% have reported a lack of confidence with daytime driving and 88% have reported a lack of confidence with nighttime driving.²

Given its effect on the quality of life, patients rank severe (VA $\leq$ 20/200) and very severe (VA $\leq$ 20/800) vision loss due to AMD among the worst diseases.³ They compare such vision loss to home dialysis, uncontrollable pain due to cancer, and even stroke resulting in permanent bedridden status.

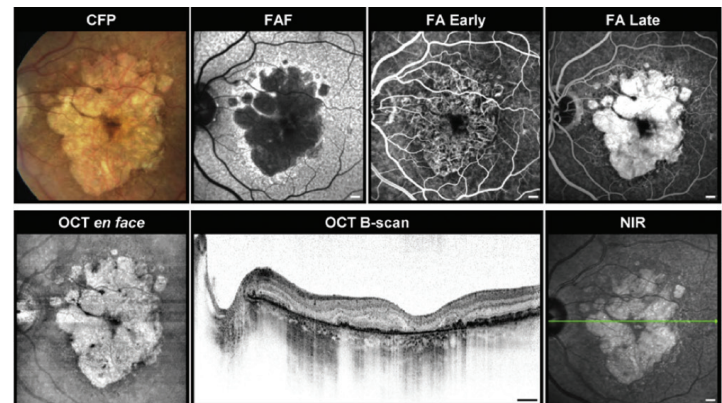
It is estimated that more than 3.5 million patients in the United States will have AMD by the year 2030; that number is estimated to rise to 5 million by 2050.⁴ As the number of patients in our clinics increases in the coming decades and as we, hopefully, have treatments for GA, it will be important to understand how the disease is classified, how disease progression is quantified, and the best ways to assess visual loss due to GA. This will allow us to study the effects and outcomes of the potential therapeutics and identify patients at highest risk of progression who might benefit the most from early interventions.

CLASSIFICATION AND RISK FACTORS FOR GA

The Beckman Initiative for Macular Research Classification Committee categorized AMD into four stages: (1) no AMD; (2) early AMD; (3) intermediate AMD; (4) and advanced AMD.⁵ The two forms of advanced AMD are neovascular AMD (also called wet AMD) and GA.

A patient is classified as having no AMD when no pigmentary abnormalities are observed and no or only few druselets ($\leq 63 \mu\text{m}$ drusen) are detected.⁵ Patients with early AMD show no pigmentary changes and demonstrate drusen between $63 \mu\text{m}$ and $125 \mu\text{m}$ in size. When at least one drusen greater than $125 \mu\text{m}$ is observed, or when pigmentary changes are seen, a patient has intermediate AMD. (In the clinic, it may be useful to use the central retinal vein for measuring drusen, as this vein is approximately $125 \mu\text{m}$.)

Central vision loss associated with macular damage is the hallmark of advanced AMD.⁵ If neovascularization is observed, then the patient is diagnosed with wet AMD. Patients with GA



Fleckenstein M, Mitchell P, Freund KB, et al. *Ophthalmology*. 2018;125(3):369-390.

Figure 1. GA is conducive to multimodal imaging. Lesions can be observed on CFP, FAF, NIR, and en face OCT imaging, and tissue layer loss is seen on OCT B-scan.¹³

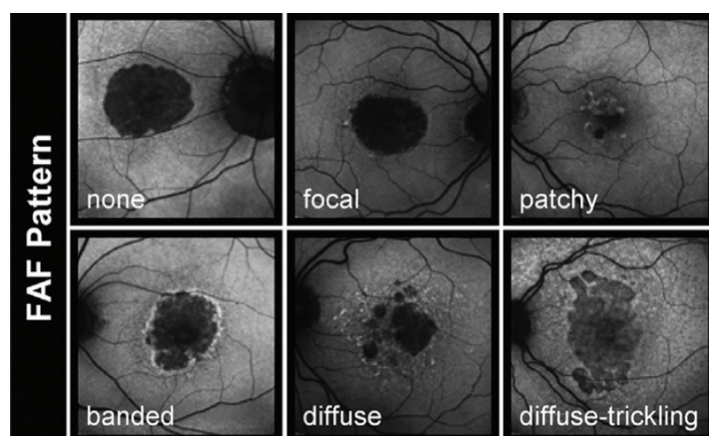
demonstrate loss of photoreceptors, thinning the retinal pigment epithelium (RPE) and choriocapillaris layers, and resultant dense scotomas.⁶

Smoking history and age have been tied to GA development.⁷⁻¹⁰ A history of 40 pack-years of cigarettes has been tied to a 3.4-fold increase of risk of GA development.¹⁰ Patients who are older than 90 have a significantly higher prevalence of GA compared with those who are 84 and younger.^{8,9} Risk factors for development of AMD in general include family history of AMD, smoking history, obesity, and hypertension.¹¹

CLINICAL PRESENTATION

GA can be observed on a number of imaging modalities (Figure 1). Imaging reports may be handy tools for educating patients and their family about disease progression, identifying patients who are at highest risk for progression, and also for assessing the effects of potential therapeutics. The most commonly used imaging modalities in clinical practice and research are optical coherence tomography (OCT), color fundus photography (CFP), and fundus autofluorescence (FAF). The role of other imaging modalities such as OCT angiography and confocal near-infrared reflectance is being investigated.

B-scan OCT imaging is what most physicians use in clinic. It depicts loss of outer retinal layers corresponding to the RPE and photoreceptors. En face OCT imaging can be used to educate the patients in clinic environment. CFP has been used in earlier clinical studies with FAF being a current go-to modality to assess GA. CFP shows sharply demarcated hypopigmented unifocal or



Fleckenstein M, Mitchell P, Freund KB, et al. *Ophthalmology*. 2018;125(3):369-390. Holz FG, Bindewald-Wittich A, Fleckenstein M, et al; FAM-Study Group. *Am J Ophthalmol*. 2007;143(3):463-472.

Figure 2. GA lesions as detected on FAF may be classified in a number of ways. Eyes with banded and diffuse lesions are more likely to experience disease progression than eyes with other types of lesions.^{13,14}

multifocal areas with sometimes visible larger choroidal vessels due to the absence of the RPE and the choriocapillaris.¹²

Progression usually begins in the extrafoveal region and proceeds in a horseshoe pattern until the lesion is donut shaped. Foveal involvement of lesions usually occurs in the final stage of progression.

Imaging of GA lesions will be valuable in identifying patients at highest risk of progression and when tracking the anatomic outcomes of future treatments. Natural history studies have determined that the rate of lesion progression in GA patients ranges from 0.53 mm² to 2.6 mm² per year (median 1.78 mm²).^{13,14} Risk factors for faster progression include larger baseline lesion size, extrafoveal lesions, multifocal lesions, fellow eye GA, as well as some FAF patterns.^{15,16}

On FAF, hypoautofluorescent areas indicate GA lesions. The lesions can have different configurations and borders or junctional zones around the lesions can be hyperautofluorescent.¹⁷ Different FAF patterns have been implicated as risk factor for GA progression.¹³ Holz et al found that patients with GA whose lesions were classified as banded or diffuse trickling were more likely to experience disease progression compared with those whose lesions fit other classifications.¹⁴

Increased FAF as seen in the junctional zone of GA can be classified as focal, patchy, banded, or diffuse, with diffuse-trickling being one of the diffuse patterns (Figure 2). Patients with focal lesions show evidence of one or more small spots of elevated FAF at a lesion's edge, while lesions that show some FAF spots outside the GA area are classified as patchy.¹⁸ Banded patterns are defined as having central hypoautofluorescence with a hyperautofluorescent border surrounding the entire lesion.¹⁸ Patients with diffuse lesions show evidence of FAF spots outside the GA lesion area, with spread toward the posterior pole.¹⁸ Lesions that demonstrate gray (rather than black) hypoautofluorescence and lobular atrophic patches with high intensity at the margins are classified as diffuse-trickling.¹⁹

MEASURING VISUAL LOSS

The standard Snellen best corrected visual acuity (BCVA) may be an inadequate measurement of visual function in patients with GA due to the foveal-sparing nature of the disease.¹³ It does not represent the patient visual experience and assessing the efficacy of future treatments for this disease will require use of alternative visual assessments, such as microperimetry, low luminance visual acuity (LLVA), reading speed assessment, and patient-reported outcomes.¹³

Microperimetry

Microperimetry measures threshold light sensitivity at multiple points over the macula.²⁰ During a microperimetry test, patients press a button to acknowledge perception of a stimulus. A sensitivity map can be obtained by modifying the stimulus intensity. Visual field sensitivity reports from microperimetry test can be overlaid atop CFP and other imaging modalities, leading to an understanding of the relationship between anatomy and function.

Low Luminance Visual Acuity

Given that GA patients often have significant visual impairment in dimly lit settings, use of LLVA may be a reliable metric of disease progression and disease impact on visual acuity. During an LLVA assessment, a patient reads a normally illuminated ETDRS chart through a 2.0-log unit neutral density filter placed over the best correction for their eye. Sunness et al found that baseline low luminance deficit was a strong predictor of subsequent vision loss for all levels of baseline VA in patients with GA.²¹ They also found that use of LLVA could identify patients who are at the highest risk for VA loss due to GA.²¹

Reading Speed Assessment

Patients with extrafoveal GA lesions may be able to see single letters on a traditional eye chart because a single letter may fall within the foveal region. To this end, asking a patient to read an entire sentence may be a more accurate measure of visual function. These reading speed evaluations could expose a decline in visual function due to parafoveal atrophic areas.²²

Patient-reported Outcomes

The National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25) is one of the examples of an assessment by which patients may report practical visual function. It asks questions, for example, about the ability to perform daily tasks. Sivaprasad et al found that the NEI VFQ-25 was a "reliable and valid cross-sectional measure of the impact of GA on patient visual function and vision-related quality of life."²³

LEARNING TO ASSESS GA

If any of the pipeline therapies for GA achieve regulatory approval, then it will change the paradigm of how we approach our GA patients. Even now understanding how the patients' vision affects their quality of life is important. Given that the potential

treatments may prevent GA growth and rather than reverse GA damage, it will be even more essential to know how to identify patients who will benefit most from these novel treatments and how to assess response to these treatments. ■

1. Taylor DJ, Hobby AE, Binns AM, et al. How does age-related macular degeneration affect real-world visual ability and quality of life? A systematic review. *BMJ Open*. 2016;6(12):e011504.
2. Patel PJ, Ziemssen F, Ng E, et al. Burden of illness in geographic atrophy: a study of vision-related quality of life and health care resource use. *Clin Ophthalmol*. 2020;14:15-28.
3. Yuzawa M, Fujita K, Tanaka E, et al. Assessing quality of life in the treatment of patients with age-related macular degeneration: clinical research findings and recommendations for clinical practice. *Clin Ophthalmol*. 2013;7:1325-1332.
4. Age-Related Macular Degeneration (AMD) Data and Statistics. National Eye Institute. National Institutes of Health. Available at: <https://www.nei.nih.gov/learn-about-eye-health/resources-for-health-educators/eye-health-data-and-statistics/age-related-macular-degeneration-amd-data-and-statistics>. Accessed November 13, 2020.
5. 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.
6. Lindblad AS, Lloyd PC, Clemons TE, et al; Age-Related Eye Disease Study Research Group. Change in area of geographic atrophy in the Age-Related Eye Disease Study: AREDS report number 26. *Arch Ophthalmol*. 2009;127:1168-1174.
7. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2:e106-e116.
8. Age-Related Eye Disease Study Research Group. Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: Age-Related Eye Disease Study report number 3. *Ophthalmology*. 2000;107(12):2224-2232.
9. Joachim N, Mitchell P, Burlutsky G, et al. The incidence and progression of age-related macular degeneration over 15 years: the Blue Mountains Eye Study. *Ophthalmology*. 2015;122(12):2482-2489.
10. Khan JC, Thurlby DA, Shahid H, et al; Genetic Factors in AMD Study. Smoking and age related macular degeneration: the number of pack

- years of cigarette smoking is a major determinant of risk for both geographic atrophy and choroidal neovascularization. *Br J Ophthalmol*. 2006;90(1):75-80.
11. Turbert D. Top 5 risk factors for AMD. American Academy of Ophthalmology. Available at: www.aao.org/eye-health/news/top-5-risk-factors-amd. Accessed November 17, 2020. Updated January 28, 2019.
12. Sunness JS, Margalit E, Srikumaran D, et al. The long-term natural history of geographic atrophy from age-related macular degeneration: enlargement of atrophy and implications for interventional clinical trials. *Ophthalmology*. 2007;114(2):271-277.
13. Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125(3):369-390.
14. Holz FG, Bindewald-Wittich A, Fleckenstein M, 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.
15. Schmitz-Valckenberg S, Sahel JA, et al. Natural history of geographic atrophy progression secondary to age-related macular degeneration (geographic atrophy progression study). *Ophthalmology*. 2016;123(2):361-368.
16. Keenan TD, Agrón E, Domalpally A, et al; AREDS2 Research Group. Progression of geographic atrophy in age-related macular degeneration: AREDS2 report number 16. *Ophthalmology*. 2018;125(12):1913-1928.
17. Holz FG, Strauss EC, Schmitz-Valckenberg S, et al. Geographic atrophy: clinical features and potential therapeutic approaches. *Ophthalmology*. 2014;121(5):1079-1091.
18. Bindewald A, Schmitz-Valckenberg S, Jorzik JJ, et al. Classification of abnormal fundus autofluorescence patterns in the junctional zone of geographic atrophy in patients with age related macular degeneration. *Br J Ophthalmol*. 2005;89(7):874-878.
19. Fleckenstein M, Schmitz-Valckenberg S, Lindner M, et al. Fundus Autofluorescence in Age-Related Macular Degeneration Study Group. The "diffuse-trickling" fundus autofluorescence phenotype in geographic atrophy. *Invest Ophthalmol Vis Sci*. 2014;55(5):2911-2920.
20. Sadda SR, Chakravarthy U, Birch DG, et al. Clinical endpoints for the study of geographic atrophy secondary to age-related macular degeneration. *Retina*. 2016;36(10):1806-1822.
21. Sunness JS, Rubin GS, Broman A, Applegate CA, Bressler NM, Hawkins BS. Low luminance visual dysfunction as a predictor of subsequent visual acuity loss from geographic atrophy in age-related macular degeneration. *Ophthalmology*. 2008;115(9):1480-1488.e1-2.
22. Lindner M, Plau M, Czuderna J, et al. Determinants of reading performance in eyes with foveal-sparing geographic atrophy. *Ophthalmol Retina*. 2019;3(3):201-210.
23. Sivaprasad S, Tschosik E, Kapre A, et al. Reliability and Construct validity of the NEI VFQ-25 in a subset of patients with geographic atrophy from the phase 2 Mahalo study. *Am J Ophthalmol*. 2018;190:1-8.

A Hypothesis on the Pathophysiology of Geographic Atrophy Based on the Complement System

The pathogenesis of GA may be related to the complement system.

CAROLINE R. BAUMAL, MD

By understanding some of the contributing factors involved in the pathogenesis of intermediate and advanced age-related macular degeneration (AMD), clinicians will have a better understanding how modifiable factors may play a role in disease development—and how pharmaceutical innovations may eventually help patients with geographic atrophy (GA).

DRUSEN MAKEUP

As mentioned by my colleague Aleksandra Rachitskaya, MD, in the previous article, a patient is considered to have intermediate AMD when at least one drusen is observed that measures at least 125 μm .¹ Drusen are extracellular deposits below the RPE comprising lipid- and protein-rich debris.² Drusen are comprised of approximately 40% lipid,³ and contain a number of other components including lipofuscin, albumin, apolipoprotein E, and immunoglobulins.² Complement components such as C1q C3, C5, and C3b-9 have also been detected in drusen, implicating

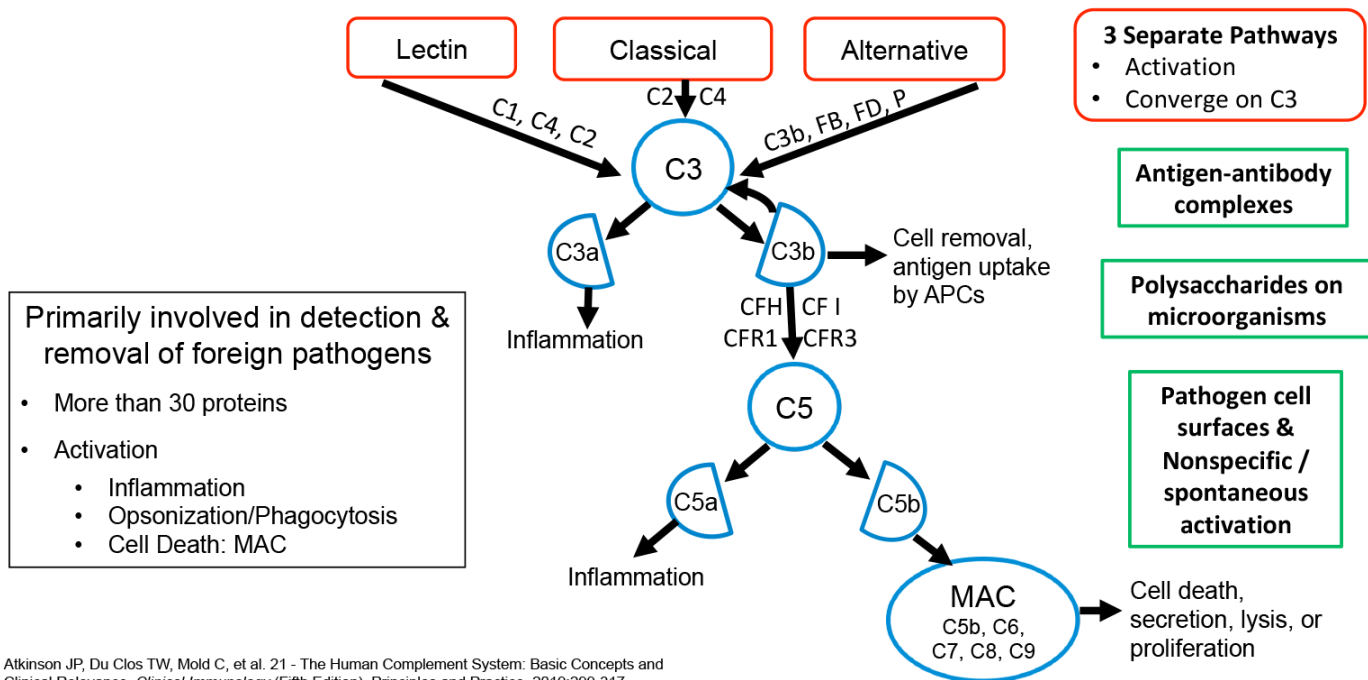
the potential role of the complement cascade in the pathogenesis of GA.²

RISK FACTORS

Risk factors for development of AMD may be classified as modifiable or nonmodifiable.

Modifiable risk factors include smoking status and diet. Advanced AMD is associated with current smoking status,⁴ and predictive models have found that smoking history may determine risk of visual loss secondary to advanced AMD.⁵ The Age-Related Eye Disease Study Group found that patients who smoked were more likely to develop GA compared with non-smokers.⁶ A healthy diet that includes fruit, vegetables, fish, and legumes has been associated with lower incidence of AMD.⁷

As may be expected for an age-related disorder, age is a relevant risk factor associated with development of AMD.^{6,8} Approximately two-thirds of patients with AMD are women,⁹ and Caucasian



Atkinson JP, Du Clos TW, Mold C, et al. 21 - The Human Complement System: Basic Concepts and Clinical Relevance. *Clinical Immunology* (Fifth Edition). Principles and Practice. 2019:299-317.

Figure 1. The complement system's activation of C3 via any of the three complement pathways (ie, classical, lectin, and alternative) leads to a cascade of events that results in inflammation, formation of MAC, and removal of cellular debris. Dysregulation of the complement system is implicated in the formation of GA, as supported by the complement components found in drusen.

individuals experience a higher incidence of AMD compared with non-Caucasian races.⁹ Family history is positively associated with development of AMD.

Ocular history is generally a nonmodifiable status that may interact with another nonmodifiable risk factor: genetic makeup. Pseudophakic and aphakic status has been associated with increased risk of developing AMD in patients with a particular genetic profile in a 2015 study.¹¹ Researchers in that study examined patients with particular genetic polymorphisms on the CFH and ARMS2 risk alleles. These two alleles have been linked with AMD in a number of studies.¹²⁻¹⁴

Over 40 genetic loci have been implicated in AMD, accounting for approximately 50% of the risk for developing disease. These genetic variants may predict increased activation or decreased inactivation of the complement cascade, which may in turn lead to excessive inflammatory activity. Indeed, the risk alleles CFH and ARMS2 have been independently associated with complement activation.¹⁴ In a study that compared patients with AMD to age-matched controls, patients with disease who had either or both risk alleles were significantly more likely to have complement component ratios that indicated C3 activation.¹⁴ The same study also found that activation of the alternative complement pathway was significantly higher in AMD patients, and that levels of complement activation components C3d, C5a, and CFB were all significantly higher in patients with disease.¹⁴

HYPOTHESIS ON GA'S RELATIONSHIP TO THE COMPLEMENT PATHWAY

An understanding of the complement pathway's role in AMD

may help illustrate why targeting specific elements of the complement cascade could lead to therapeutic benefit for patients.

A current hypothesis regarding the pathophysiology of GA considers that oxidative stress, genetic predisposition, and environmental factors (including the aforementioned modifiable risk factors such as smoking status and diet) play a role in complement deposition between the retinal pigment epithelium (RPE) and Bruch membrane.¹⁵ GA occurs after complement regulation is lost and a breakdown of the blood-retinal barrier occurs.²

The complement pathway—so named because it complements the antibody system in the body's immune response—is a first-line defense meant to protect the body against invasive microorganisms.¹⁶ It is a means of innate immunity that does not change as we age.

The complement system consists of a series of cascade reactions.¹⁶ Three separate pathways (lectin, classical and alternative) all converge onto C3. Activation of C3 leads to its cleavage into C3a and C3b (which may autoregulate back to C3), which in turn, activates C5 (Figure 1). The cleavage of C5 into C5a and C5b results in the latter component forming membrane attack complex (MAC), which is responsible for death of pathogenic cells in a functioning complement pathway.¹⁶ It is theorized that inappropriate overactivation of the complement system may contribute to AMD pathogenesis.¹⁷

The complement system as illustrated in Figure 1 is a simplified schematic of a complex cascade matrix. More than 30 proteins and protein fragments play a role in the complement system. The complement cascade contains many potential spots where the cascade can be interrupted. Therapy at the complement level may seek

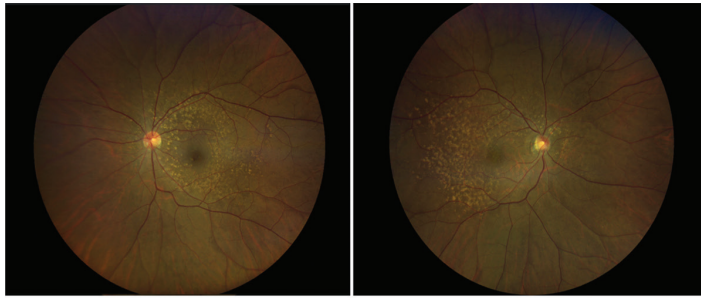


Figure 2. Fundus photography of a 40-year-old patient with a history of complement-mediated IgA nephropathy who presented with abnormalities detected on routine retinal examination. SDDs similar to those in patients with intermediate AMD were noted.

to establish which points of intervention maximize therapeutic outcomes while minimizing other effects. Roger A. Goldberg, MD, MBA, discusses this topic further in the final article of this series.

Three pathways in the complement system—the classical, lectin, and alternative pathways—all activate C3.¹⁶ Histopathologic studies of eye with AMD using confocal immunofluorescence microscopy have shown that C3 and C5 accumulate in drusen found in the sub-RPE space.^{18,19}

David Lally, MD, and I reported a case that illustrates the relationship between overactivation of the complement system and sub-RPE drusen-like deposits (DLD).²⁰ A 40-year-old woman presented to the eye clinic with no visual symptoms and fundus abnormalities were observed during a routine eye exam. Subretinal drusenoid deposits (SDDs) were detected on fundus imaging (Figure 2). These deposits were observed to be below the RPE on OCT imaging. The patient's medical history was noteworthy for stage 3 kidney disease secondary to IgA nephropathy. Renal biopsy detected C1q and C3 in the patient's mesangial IgA deposits, both of which have been shown to compose part of drusen in patients with GA.² Given that the patient was unlikely to have AMD at the age of 40, it seems the patient's complement-driven kidney disease was tied to her ophthalmic presentation.

WHAT'S NEXT?

The targeting of specific steps in the complement cascade may provide therapeutic benefit to inhibit retinal damage in individuals with GA. A discussion of pipeline therapies to target the complement system appears later in this series. ■

1. 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.
2. Ambati J, Atkinson JP, Gelfand BD. Immunology of age-related macular degeneration. *Nat Rev Immunol*. 2013;13(6):438-451.
3. Wang L, Clark ME, Crossman DK, et al. Abundant lipid and protein components of drusen. *PLoS One*. 2010;23(5(4)):e10329.
4. Joachim N, Mitchell P, Burlutsky G, Kifley A, Wang JJ. The incidence and progression of age-related macular degeneration over 15 years: the Blue Mountains Eye Study. *Ophthalmology*. 2015;122(12):2482-2489.
5. Seddon JM, Rosner B. Validated prediction models for macular degeneration progression and predictors of visual acuity loss identify high-risk individuals. *Am J Ophthalmol*. 2019;198:223-261.
6. Age-Related Eye Disease Study Research Group. Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: Age-Related Eye Disease Study report number 3. *Ophthalmology*. 2000;107(12):2224-2232.
7. Merle BM, Colijn JM, Cougnard-Gregoire A, et al; EYE-RISK Consortium. Mediterranean diet and incidence of advanced age-related macular degeneration: the EYE-RISK consortium. *Ophthalmology*. 2019;126(3):381-390.
8. Klen R, Klein BE, Knudtson MD, Meuer SM, Swift M, Gangnon RE. Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. *Ophthalmology*. 2007;114(2):253-262.
9. Age-Related Macular Degeneration (AMD) Data and Statistics. National Eye Institute. National Institutes of Health. Available at: <https://www.nei.nih.gov/about-eye-health/resources-for-health-educators/eye-health-data-and-statistics/age-related-macular-degeneration-amd-data-and-statistics>. Accessed November 13, 2020.
10. Al-Zamil WM, Yassin SA. Recent developments in age-related macular degeneration: a review. *Clin Interv Aging*. 2017;22:1313-1330.
11. Wong CW, Liao J, Cheung GC, et al. Lens status influences the association between CFH polymorphisms and age-related macular degeneration: findings from two population-based studies in Singapore. *PLoS One*. 2015;10(3):e0119570.
12. Varvas DG, Small KW, Awh CC, et al. CFH and ARMS2 genetic risk determines progression to neovascular age-related macular degeneration after antioxidant and zinc supplementation. *Proc Natl Acad Sci U S A*. 2018;115(4):E696-E704.
13. Awh CC, Lane AM, Hawken S, et al. CFH and ARMS2 genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration. *Ophthalmology*. 2013;120(11):2317-2323.
14. Smalldozic D, Klaver CCW, Klevering J, et al. Risk alleles in CFH and ARMS2 are independently associated with systemic complement activation in age-related macular degeneration. *Ophthalmology*. 2012;119(2):339-346.
15. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol*. 2011;119(10):1417-1436. Erratum in: *Arch Ophthalmol*. 2008;126(9):1251.
16. Atkinson JP, Du Clos TW, Mold C, et al. 21 - The Human Complement System: Basic Concepts and Clinical Relevance. Clinical Immunology (Fifth Edition). *Principles and Practice*. 2019:299-317.
17. Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, et al. The pathophysiology of geographic atrophy secondary to age-related macular degeneration and the complement pathway as a therapeutic target. *Retina*. 2017;37(5):819-835.
18. Anderson DH, Mullins RF, Hageman GS, Johnson LV. A role for local inflammation in the formation of drusen in the aging eye. *Am J Ophthalmol*. 2002;134(3):411-431.
19. Anderson DH, Radeke MJ, Gallo NB, et al. The pivotal role of the complement system in aging and age-related macular degeneration: hypothesis re-visited. *Prog Retin Eye Res*. 2010;29(2):95-112.
20. Lally DL, Bauman C. Subretinal drusenoid deposits associated with complement-mediated IgA nephropathy. *JAMA Ophthalmol*. 2014;132(6):775-777.

The Role of Imaging in Geographic Atrophy

Armed with the knowledge of how to image GA, clinicians may be able to track disease progression.

SRINAVAS SADDA, MD

The Classification of Atrophy Meeting (CAM) published a consensus paper on “imaging modalities used to detect and quantify atrophy due to late-stage non-neovascular and neovascular age-related macular degeneration (AMD).”¹ As treatments for geographic atrophy (GA) make their way

through the pipeline—and hopefully into the clinic—it behooves retina specialists to know the benefits of various imaging modalities as they relate to GA. Here, I will summarize a few of them, which includes some of the findings of the CAM group.

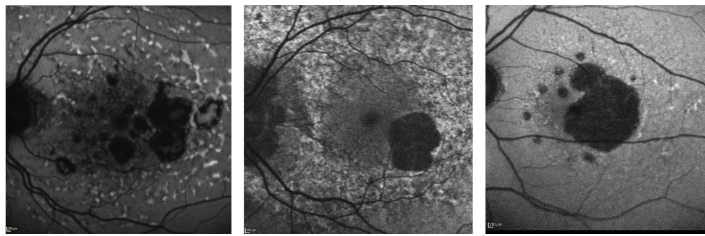


Figure 1. Clinicians must be able to distinguish diseases such as late-onset Stargardt disease (left) and pentosan polysulfate-induced maculopathy (center) from GA (right) on FAF imaging.

ADVANCES IN COLOR FUNDUS PHOTOGRAPHY

Flash color fundus photography (CFP) has been the gold standard of GA diagnosis for several decades.²⁻⁴ GA on CFP is identified by sharply demarcated borders, depigmentation, and increased visibility of the choroidal vessels. CFP requires good stereopsis and contrast in order to get a reliable determination of atrophy borders. This can be challenging to achieve consistently, however, in clinical practice.

Confocal CFP (either based on white light or scanning laser ophthalmoscopy) and multicolor CFP have improved the contrast of images; enhanced contrast is especially obvious in patients with media opacity. My colleagues and I asked reading center graders to interpret images captured by confocal CFP, flash CFP, and fundus autofluorescence (FAF).⁵ We found that although flash CFP, confocal CFP, and FAF were all similar in their measurements of atrophy, confocal CFP produced better grading reproducibility than flash CFP. We concluded that confocal CFP was a possible useful tool to quantitatively monitor GA lesions.⁵

FUNDUS AUTOFLUORESCENCE

FAF can be used to image atrophic lesions in GA patients. It is particularly useful in improving contrast for visualizing the extent of the GA lesion and for classifying the pattern of increased fluorescence at the border of the GA lesion as described by Aleksandra Rachitskaya, MD, in a previous article in this series. Enlargement of GA lesion size on FAF has been used as an outcome measure in a number of clinical trials.⁶⁻⁹ Limitations related to FAF include the need for specialized autofluorescence technology and the relative discomfort of the imaging test itself, as some patients may find the intensity of light required to obtain the autofluorescence signal bothersome.

To illustrate the clinical value of FAF, refer to Figure 1. All of the images captured in this figure are from 70-year-old patients. Retina specialists relying on FAF to diagnose patients with GA should be prepared to distinguish GA from other atrophy-inducing conditions. The image on the left panel of Figure 1 depicts late-onset Stargardt disease, as evidenced by the flecks of hyperautofluorescence near the broader areas of atrophy. The image in the center of Figure 1 may at first appear to be advanced AMD, but further consideration of the region of mottled autofluorescence near the area of atrophy should lead to the correct diagnosis of pentosan polysulfate-induced maculopathy. The diffuse pattern of atrophy found on the right panel of Figure 1 aligns with

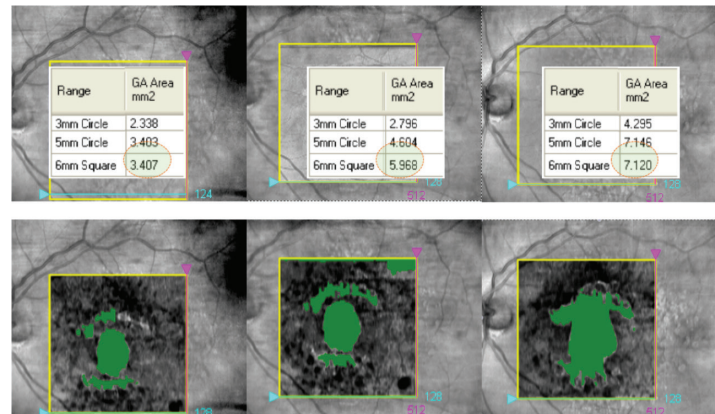


Figure 2. Software allows automatic calculation of the hypertransmission area on OCT (corresponding to the GA), which may be useful in tracking disease progression in some patients.

the traditional presentation of GA on FAF (ie, obvious regions of hypoautofluorescence and no characteristic patterns of hyperautofluorescence to suggest an alternative diagnosis). This is the type of patient who should be considered for a clinical trial for GA—or, if future therapies are approved, treatment for their condition.

OPTICAL COHERENCE TOMOGRAPHY

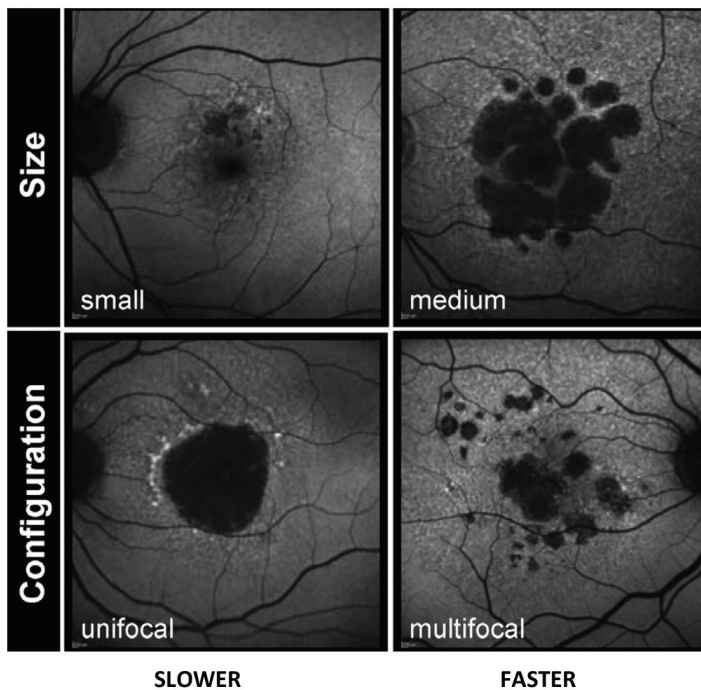
Optical coherence tomography (OCT) platforms are more ubiquitous than FAF platforms in ophthalmology clinics and may be more comfortable for patients compared with FAF. Indeed, OCT is the imaging modality of choice in my clinic due to its speed, comfort, and ability to quickly track lesion size changes over time. Potential regions of atrophy on OCT are most readily identified by areas increased brightness of the underlying choroid due to the hypertransmission of light through retinal tissue. These regions of hypertransmission may be quantified by automatic tools in the OCT software (Figure 2).

However, one caveat to this approach is that not all regions of hypertransmission may reflect a complete atrophy of the overlying outer retina—it may be partial or only nascent atrophy, for example. A challenge at the time was lack of a consensus for defining atrophy on OCT, which led to the creation of the CAM.^{1,10}

The CAM published a report that defined a new term: cRORA, or complete retinal pigment epithelium (RPE) and outer retinal atrophy.¹⁰ A patient has cRORA if, on OCT imaging, they demonstrate a hypertransmission area of at least 250 μm and a zone of RPE attenuation of at least 250 μm .¹⁰ Patients with cRORA must also show evidence of overlying photoreceptor degeneration that may be evidenced by thinning of the outer nuclear layer, loss of the external limiting membrane, and/or loss of the ellipsoid zone/interdigitation zone.¹⁰ Patients with atrophy due to an RPE tear are excluded. It should be noted that under this classification system, GA is a subset of cRORA that represents atrophy in the absence of neovascularization.¹⁰

PROGNOSTICATION

Fleckenstein et al summarized how findings on FAF and OCT can be used to predict progression of GA in patients.¹¹ As we move toward



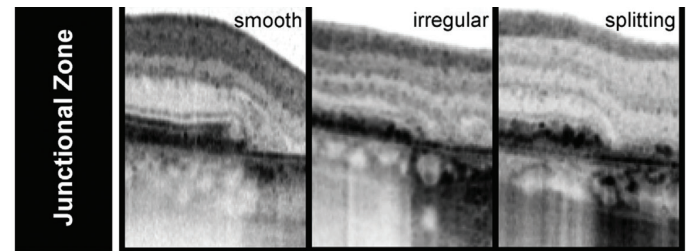
Fleckenstein M, Mitchell P, Freund KB, et al. *Ophthalmology*. 2018;125(3):369-390.

Figure 3. GA lesion size and configuration help predict which patients are at risk for faster disease progression.

the possibility of approved treatments for GA, it may be important to identify which patients are at the highest risk for rapid progression and are therefore most likely to benefit from intervention.

GA lesions on FAF that are larger or are multifocal are more likely to rapidly progress compared with those that are smaller or unifocal,¹¹ perhaps due to their larger perimeter, as GA lesions enlarge from their borders (Figure 3). Bindewald et al found that lesions with a hyperautofluorescent band surrounding the margin of lesion (termed a banded pattern) or extensive autofluorescence changes at the margin and beyond the GA lesion (termed diffuse patterns, of which diffuse trickling was the most rapid) were more likely to progress rapidly than other lesions, such as those with only tiny/focal regions or without any hyperfluorescence at the margin (ie, not as severely abnormal as those depicted in Figure 1).¹²

OCT findings can also be used to predict disease progression. Detection on OCT of a thin choroid or reticular pseudodrusen (also called subretinal drusenoid deposits) are also risk factors for faster GA progression.¹¹ Nunes et al found that darkened areas surrounding GA lesions as detected on en-face OCT at the level of the photoreceptors were predictive of quicker lesion growth.¹³ Disruption of the RPE band near the border of GA lesions as



Fleckenstein M, Mitchell P, Freund KB, et al. *Ophthalmology*. 2018;125(3):369-390.

Figure 4. Disruption of the outer retinal layers at the margins of the lesion as seen on OCT may be associated with faster GA progression.

observed on OCT, particularly if the Bruch's membrane is split by the RPE, may also predict more rapid progression (Figure 4).¹¹

THE VALUE OF IMAGING

Optimally utilizing imaging to diagnose and prognosticate GA in our patients will be paramount to providing the best care as we move toward regulatory approval for GA therapies. CFP, FAF, and OCT all offer different means by which to image our patients with GA, providing us information to better manage them going forward. ■

- Holz FG, Sadda SR, Staurenghi G, et al. CAM group. Imaging protocols in clinical studies in advanced age-related macular degeneration: recommendations from classification of atrophy consensus meetings. *Ophthalmology*. 2017;124(4):464-478.
- Schmitz-Valckenberg S, Sahel JA, Danis R, et al. Natural history of geographic atrophy progression secondary to age-related macular degeneration (Geographic Atrophy Progression Study). *Ophthalmology*. 2016;123:361-368.
- Chew EY, Clemons T, Sangiovanni JP, et al. The Age-Related Eye Disease Study 2 (AREDS2): study design and baseline characteristics (AREDS2 report number 1). *Ophthalmology*. 2012;119:2282-2289.
- Gunwaldt JE, Daniel E, Ying GS, et al. Photographic assessment of baseline fundus morphologic features in the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2012;119:1634-1641.
- Lei J, Al-Sheikh M, Shi Y, et al. Reliability of confocal white-light fundus imaging for measurement of retinal pigment epithelial atrophy in age-related macular degeneration. *Retina*. 2018;38(10):1930-1936.
- Holz FG, Sadda SR, Busbee B, et al. the Chroma and Spectri Study Investigators. Efficacy and safety of lapanizumab for geographic atrophy due to age-related macular degeneration. Chroma and Spectri phase 3 randomized clinical trials. *JAMA Ophthalmol*. 2018;136(6):666-677.
- Rosenfeld PJ, Dugel PU, Holz FG, et al. Emsixstat hydrochloride for geographic atrophy secondary to age-related macular degeneration: a randomized clinical trial. *Ophthalmology*. 2018;125(10):1556-1567.
- CLG561 proof-of-concept study as a monotherapy and in combination with LFG316 in subjects with geographic atrophy (GA). ClinicalTrials.gov Identifier: NCT02515942. Available at: <https://clinicaltrials.gov/ct2/show/NCT02515942>. Accessed December 28, 2020.
- Evaluation of oral minocycline in the treatment of geographic atrophy associated with age-related macular degeneration. ClinicalTrials.gov Identifier: NCT02564978. Available at: <https://clinicaltrials.gov/ct2/show/NCT02564978>. Accessed December 28, 2019.
- Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on ocr: classification of atrophy report 3. *Ophthalmology*. 2018;125(4):537-548.
- Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125(3):369-390.
- Bindewald A, Schmitz-Valckenberg S, Jorzik JJ, et al. Classification of abnormal fundus autofluorescence patterns in the junctional zone of geographic atrophy in patients with age related macular degeneration. *Br J Ophthalmol*. 2005;89(7):874-878.
- Nunes RP, Gregori G, Yehoshua Z, et al. Predicting the progression of geographic atrophy in age-related macular degeneration with SD-OCT en face imaging of the outer retina. *Ophthalmic Surg Lasers Imaging Retina*. 2013;44(4):344-359.

Approaches to Treatment in Geographic Atrophy

A review of potential therapeutic strategies for GA.

ROGER A. GOLDBERG, MD, MBA

There are no approved treatments for geographic atrophy (GA). However, there are a number of pipeline therapies that may achieve regulatory approval. I will review various pathways that these therapies target for potential treatment of this progressive and blinding disease.

COMPLEMENT INHIBITION

In a previous article in this series, Caroline Bauman, MD, reviewed the complement system's role in GA formation and progression. Overactivation of the complement system leads to the creation of C3, which in turn activates a cascade that produces inflammatory mediators such as C3a and C5a.^{1,2} The cascade reaction also leads to the formation of membrane attack complex (MAC), which is responsible for cell lysis. Given that the three complement pathways—classical, lectin, and alternative—all lead to the production of C3,¹ inhibition of C3 is a natural target for a potential GA treatment. Positive phase 2 data from trials evaluating pegcetacoplan (Apellis Pharmaceuticals)^{3,4} for the treatment of GA via targeting C3 has led to the initiation of a pair of phase 3 trials.^{5,6}

Targeting C5, which is downstream of C3, may also be an effective target for GA therapy, as doing so may prevent the formation of C5a and MAC. Avacincaptad pegol is under investigation in the phase 2b/3 GATHER1 and GATHER2 studies,^{7,8} the former of which met its prespecified primary endpoint.⁹ Prior therapeutics targeting the complement pathway have not been able to demonstrate an ability to slow the progression of GA. The largest of these unsuccessful clinical trial programs was a complement factor D inhibitor (lampalizumab),¹⁰ though prior efforts targeting C5 also have not shown a positive effect.¹¹

Because of the complement system's role in fighting infection, one concern with suppressing complement is the potential, in theory, to increase a patient's susceptibility to infection. In addition, earlier-stage clinical trials have suggested that complement inhibition may either increase or unmask choroidal neovascularization.^{3,4} If a complement-based therapy is approved for treatment, clinicians will need to decide when to initiate treatment, and monitor for potential side effects to ensure that they uphold their duty to "first, do no harm."

STEM CELLS

Stem cells represent some of the most cutting-edge technology

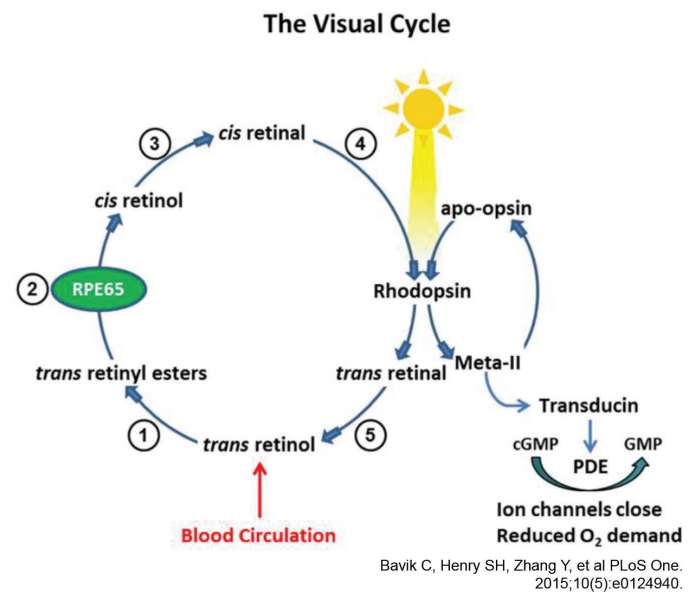


Figure. The elimination of toxic byproducts in the visual cycle may be an effective strategy for GA treatment, but interference with normal retinal function is a concern.

in regenerative medicine. Stem cell therapy for GA could be used for regeneration of retinal tissue (and thus potentially for reversal of GA), or for stalling progression of GA lesions.

Regenerative strategies aim to replace the lost retinal pigment epithelial (RPE) cells that support overlying photoreceptors or to initiate migration of photoreceptors to areas of atrophy. Such moves hope to restore vision that has been lost due to disease proliferation. Alternatively, stem cells could be used to stave off further vision loss. Placing healthy RPE cells near native photoreceptors and RPE cells could support native tissue and slow vision loss. Allogenic stem cells, which come from a single source, may have a high risk of rejection but may be more shelf stable. Autologous stem cells, which are derived from a patient's own tissue, may be more difficult to produce but carry a lower risk of rejection.

Delivery of stem cell therapy to the posterior segment is a challenge. Surgical approaches require vitrectomy, retinectomy, and placement of cells into the subretinal space (ie, transretinal delivery. Suprachoroidal approaches require a Bruch membranectomy

after entry into the suprachoroidal space and placement of cells into the subretinal space (ie, transchoroidal delivery). Although the transretinal approach may be more familiar to retinal surgeons, one concern is that the RPE cells could migrate onto the retinal surface, causing epiretinal membrane formation or proliferative vitreoretinopathy.^{12,13}

Theoretical concerns about tumorigenicity have not manifested in patients to date.¹³ Patients must be educated about the dangers of cash-pay clinics offering stem cell therapy, as a number of these facilities have misled patients into believing that current technology is safe and efficacious when, in fact, patients in these clinics have often ended up effectively blind due to a series of postsurgical anatomic complications such as epiretinal membranes and retinal detachments.¹⁴

VISUAL CYCLE MODULATION

The visual cycle is depicted in Figure 1. The accumulation of toxic byproducts such as lipofuscin and A2E place stress on retinal tissue,¹⁵ and decreasing the volume of such toxins may be an effective strategy to target GA. However, slowing down the visual cycle can interfere with normal functioning. For example, in a phase 2b/3 study of emixustat, an RPE65 inhibitor, delayed dark adaptation occurred in 55% of patients.¹⁶ Fenretinide,¹⁷ which sought to prevent delivery of retinol to retinal tissue, like emixustat, failed to slow the progression of GA.

NEUROPROTECTION AND OTHER APPROACHES

Addressing mitochondrial dysfunction could help protect retinal tissue. Photobiomodulation (PBM) relies on light from LEDs to penetrate tissue and “[stimulate] cellular function via activation of photoacceptors.”¹⁸ Merry et al found that PBM resulted in anatomic and functional improvements in patients with GA.¹⁸ Further studies are ongoing.¹⁹ Drugs addressing mitochondrial dysfunction such as elamipretide and alpha-2 adrenergic agonists such as brimonidine are also under investigation for neuroprotection in GA.

Other novel approaches to GA therapy include modulation of choroidal blood flow, dosage of the antioxidant metformin, and use of statins and doxycycline.^{20,21}

DAWN OF A NEW ERA?

In the early 2000s, no restorative treatments existed for wet AMD—and then the anti-VEGF era ushered in a new treatment and the ability to return vision to patients with previous vision loss. Perhaps we are now at a similar timepoint for developing treatment for GA. Going forward, retina specialists may be tasked with determining which GA patients are best suited for intervention and choosing treatment strategies that maximize outcomes while reducing patient burden—a task similar to what we face with wet AMD therapy today. ■

- Atkinson JP, Du Clos TW, Mold C, et al. 21 - The Human Complement System: Basic Concepts and Clinical Relevance. *Clinical Immunology (Fifth Edition), Principles and Practice*. 2019:299-317
- Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, et al. The pathophysiology of geographic atrophy secondary to age-related macular degeneration and the complement pathway as a therapeutic target. *Retina*. 2017;37(5):819-835.
- Liao DS, Grossi FV, El Mehdi D, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: a randomized phase 2 trial. *Ophthalmology*. 2020;127(2):186-195.
- Apellis Pharmaceuticals announces 18-month results of phase 2 study (FLLY) of APL-2 in geographic atrophy [press release]. Apellis Pharmaceuticals; Crestwood, KY, and Cambridge, MA; February 22, 2018.
- Study to Compare the Efficacy and Safety of Intravitreal APL-2 Therapy With Sham Injections in Patients With Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration. *ClinicalTrials.gov* Identifier: NCT03525600. Available at: <https://clinicaltrials.gov/ct2/show/NCT03525600>. Accessed December 28, 2020.
- A Study to Compare the Efficacy and Safety of Intravitreal APL-2 Therapy With Sham Injections in Patients With Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration. *ClinicalTrials.gov* Identifier: NCT03525613. Available at: <https://clinicaltrials.gov/ct2/show/NCT03525613>. Accessed December 28, 2020.
- IVERIC bio Announces Positive Zimura 18 Month Data Supporting the 12 Month Efficacy Findings: Continuous Positive Treatment Effect with Favorable Safety Profile in Geographic Atrophy Secondary to Age-Related Macular Degeneration in a Phase 3 Trial [press release]. Iveric bio; New York, NY; June 15, 2020.
- IVERIC bio Announces First Patient Dosed in Second Zimura Phase 3 Clinical Trial for the Treatment of Geographic Atrophy Secondary to Age-Related Macular Degeneration [press release]. Iveric bio; New York, NY; June 30.
- IVERIC bio Announces Positive Zimura 18 Month Data Supporting the 12 Month Efficacy Findings: Continuous Positive Treatment Effect with Favorable Safety Profile in Geographic Atrophy Secondary to Age-Related Macular Degeneration in a Phase 3 Trial [press release]. Iveric bio; New York, NY; June 15, 2020.
- Holz FG, Sadda SR, Busbee B, et al; Chroma and Spectri Study Investigators. Efficacy and safety of lampalizumab for geographic atrophy due to age-related macular degeneration: Chroma and Spectri phase 3 randomized clinical trials. *JAMA Ophthalmol*. 2018;136(6):666-677.
- Yehoshua Z, de Amorim Garcia Filho CA, Nunes RP, et al. Systemic complement inhibition with eculizumab for geographic atrophy in age-related macular degeneration: the COMPLETE study. *Ophthalmology*. 2014;121(3):693-701.
- Wilson DJ, Neuringer M, Stoddard J, et al. Subretinal cell-based therapy: an analysis of surgical variables to increase cell survival. *Retina*. 2017;37(11):2162-2166.
- Schwartz SD, Tan G, Hosseini H, Nagiel A. Subretinal transplantation of embryonic stem cell-derived retinal pigment epithelium for the treatment of macular degeneration: an assessment at 4 years. *Invest Ophthalmol Vis Sci*. 2016;57(5):ORSFcl-9.
- Ansari ZA, Kuriyan AE, Albini TA. Unproven stem cell therapy for macular degeneration. *Oncotarget*. 2017;8(53):90636-90637.
- Bavik C, Henry SH, Zhang Y, et al. Visual cycle modulation as an approach toward preservation of retinal integrity. *PLoS One*. 2015;10(5):e0124940.
- Rosenfeld PJ, Dugel PU, Holz FG, et al. Emixustat hydrochloride for geographic atrophy secondary to age-related macular degeneration: a randomized clinical trial. *Ophthalmology*. 2018;125(10):1556-1567.
- Mata NL, Lichter JB, Vogel R, Han Y, Bui TV, Singerman LJ. Investigation of oral fenretinide for treatment of geographic atrophy in age-related macular degeneration. *Retina*. 2013;33(3):498-507.
- Merry GF, Munk MR, Dotson RS, Walker MG. Photobiomodulation reduces drusen volume and improves visual acuity and contrast sensitivity in dry age-related macular degeneration. *Acta Ophthalmol*. 2017;95(4):e270-e277.
- Study of Photobiomodulation to Treat Dry Age-Related Macular Degeneration (LIGHTSITE III). *ClinicalTrials.gov* Identifier: NCT04065490. Available at: <https://clinicaltrials.gov/ct2/show/NCT04065490>. Accessed December 29, 2020.
- Clinical Study to Evaluate Treatment With ORACEA for Geographic Atrophy (TOGA) (TOGA). *ClinicalTrials.gov* Identifier: NCT01782989. Available at: <https://clinicaltrials.gov/ct2/show/NCT01782989>. Accessed January 4, 2020.
- Ammar M, Chiang A. What's Ahead for the Treatment of Dry AMD. Published March 7, 2020. Available at: <https://www.reviewofophthalmology.com/article/whats-ahead-for-the-treatment-of-dry-amd>. Accessed January 4, 2021.

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Full Name _____

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DEMOGRAPHIC INFORMATION

Profession	Years in Practice	Patients Seen Per Week (with the disease targeted in this activity)	Region	Setting	Models of Care
___ MD/DO	___ >20	___ 0	___ Northeast	___ Solo Practice	___ Fee for Service
___ OD	___ 11-20	___ 1-15	___ Northwest	___ Community Hospital	___ ACO
___ NP	___ 6-10	___ 16-30	___ Midwest	___ Government or VA	___ Patient-Centered Medical Home
___ Nurse/APN	___ 1-5	___ 31-50	___ Southeast	___ Group Practice	___ Capitation
___ PA	___ <1	___ >50	___ Southwest	___ Other	___ Bundled Payments
___ Other				___ I do not actively practice	___ Other

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Describe the prevalence of age-related macular degeneration 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 evaluate the functional and anatomic outcomes used in managing patients with 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. GA accounts for what percentage of legal blindness in North America?
 - a) 5%
 - b) 10%
 - c) 20%
 - d) 33%
3. What is the most important risk factor for developing GA?
 - a) Smoking
 - b) Increasing age
 - c) Family history
 - d) Female gender
4. 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.
5. The lectin, classical, and alternative complement pathways all converge on what molecule?
 - a) Complement Factor H
 - b) Complement Factor 3
 - c) Complement Factor 5
 - d) Membrane attack complex
6. All of the following are risk factors for faster GA lesion size growth EXCEPT:
 - a) Larger lesions
 - b) Multifocal lesions
 - c) Presence of reticular pseudodrusen
 - d) Focal hyperautofluorescence at edge of lesion

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 opportunity (patients)	____ No barriers
____ Lack of consensus or professional guidelines	____ Reimbursement/insurance issues	Other. Please specify: _____
____ Lack of administrative support	____ Lack of resources (equipment)	_____
____ Lack of experience		_____
____ Lack of time to assess/counsel patients	____ Patient compliance issues	

The design of the program was effective for the content conveyed.	____ Yes ____ No	The content was relative to your practice.	____ Yes ____ No
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The content supported the identified learning objectives.	____ Yes ____ No	The faculty was effective.	____ Yes ____ No
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The content was free of commercial bias.	____ 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	____ Medical Knowledge
____ Practice-Based Learning and Improvement	____ Interpersonal and Communication Skills
____ Professionalism	____ 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: _____
