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Geographic atrophy: Mechanism of disease, pathophysiology, and role of the complement system

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Geographic atrophy: Mechanism of disease, pathophysiology, and role of the complement system

Sophie J Bakri, MD, MBA; Meryem Bektas, MBA, PhD; Darcie Sharp, PhD; Roger Luo, PhD; Sujata P Sarda, PhD; Shahnaz Khan, MPH

ABSTRACT

Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD), characterized by atrophic lesions that first start in the outer retina and progressively expand to cover the macula and the fovea, the center of the macula, leading to irreversible loss of vision over time. GA is distinct from wet or neovascular AMD (nAMD), the other form of advanced AMD. Neovascular AMD is characterized by new invading leaky blood vessels in the macula that can lead to acute vision loss. GA and nAMD may coexist in the same eye.

The underlying pathophysiology of GA is complex and thought to involve chronic inflammation due to overactivation of the complement system that leads to the loss of photoreceptors, retinal pigment epithelium (RPE), and the underlying choriocapillaris. The disappearance of these structures appears as sharply demarcated atrophic lesions that are typical of GA.

Researchers have reported about 1 million reported cases of GA in the United States, and about 160,000 cases occur per year. The most important risk factors for GA are increasing age and family history.

Diagnosis of GA is usually made by using multimodal imaging techniques. Lesions associated with GA are highly heterogeneous, and the growth rate may differ from patient to patient. Despite the progressive nature of GA, the fovea may be spared until much later in the disease, thereby retaining central vision in patients. With time, atrophic lesions may progressively grow to involve the fovea, thereby severely impairing central vision. Vision loss can happen rapidly once the lesions reach the fovea. However, even without the involvement of the fovea, ongoing vision impairment impacting daily life may be present. Median time from GA not involving the center of the fovea (without subfoveal involvement) to GA with lesion boundary affecting the foveal center (subfoveal involvement) ranges from 1.4 to 2.5 years.

GA can greatly impact patients' functioning and quality of life and limit their independence by interfering with activities of daily living, including difficulties with reading, driving, watching television, recognizing faces, and being unable to do household chores.

No treatments have been available until intravitreal pegcetacoplan was recently approved by the US Food and Drug Administration for GA secondary to AMD.

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Overview of GA

Age-related macular degeneration (AMD) has 3 distinct stages: early, intermediate, and advanced.[1] Within the advanced stage, there are 2 distinct forms: wet or neovascular AMD (nAMD) and dry AMD.[2,3] Geographic atrophy (GA) is the progressive, irreversible, advanced form of dry AMD.[4] Although the advanced form of wet AMD/nAMD is characterized by abnormal blood vessels leaking blood or other fluids into the macula, GA is characterized by atrophic lesions in the outer retina.[5,6] Although nAMD is characterized by acute vision loss, GA is a progressive disease that can lead to irreversible central blindness over time.[7] Median time to progression to legal blindness has been estimated to be 6.2 years (interquartile range [IQR] = 3.3-8.5 years).[8] Neovascular AMD can be treated with anti–vascular endothelial growth factor (VEGF) therapies to stop the leakage from blood vessels,[6] and only intravitreal pegcetacoplan, recently US Food and Drug Administration (FDA) approved, can be used to treat GA secondary to AMD.[9]

The prevalence of GA in the United States is estimated to be about 1 million people,[10] with 160,000 new cases occurring each year in the United States.[11] The average age of a patient with GA is 79 years.[12] From age 50 years, prevalence quadruples every 10 years, from 0.16% at 60 years to 2.91% at 80 years of age.[13] The incidence of GA is projected to increase in the coming decades because of an increase in the aging population.[14]

Several risk factors have been associated with GA, whereby age and family history have the strongest correlation. Smoking and genetic mutations in the complement system are additional risk factors.

Mechanism of Disease/ Pathophysiology

With aging, the retinal pigment epithelium (RPE) is exposed to intrinsic and extrinsic oxidative stressors as well as environmental stressors such as cigarette smoke. Oxidative damage accumulates, resulting in the formation of drusen, yellow deposits of lipids between the RPE and Bruch's membrane (early to intermediate AMD). The appearance and progression of drusen deposits are prognostic features of GA.[4] Excessive drusen accumulation and components of drusen, such as cellular debris, lipids, and lipoproteins, may trigger chronic inflammation via multiple pathways, including the complement cascade.[4] Chronic inflammation can eventually lead to photoreceptor, RPE, and choriocapillaris cell death, causing the appearance of sharply defined atrophic lesions, visually resembling geographic areas on a map, that are characteristic of GA and the appearance of choroidal vessels due to the missing RPE layer.

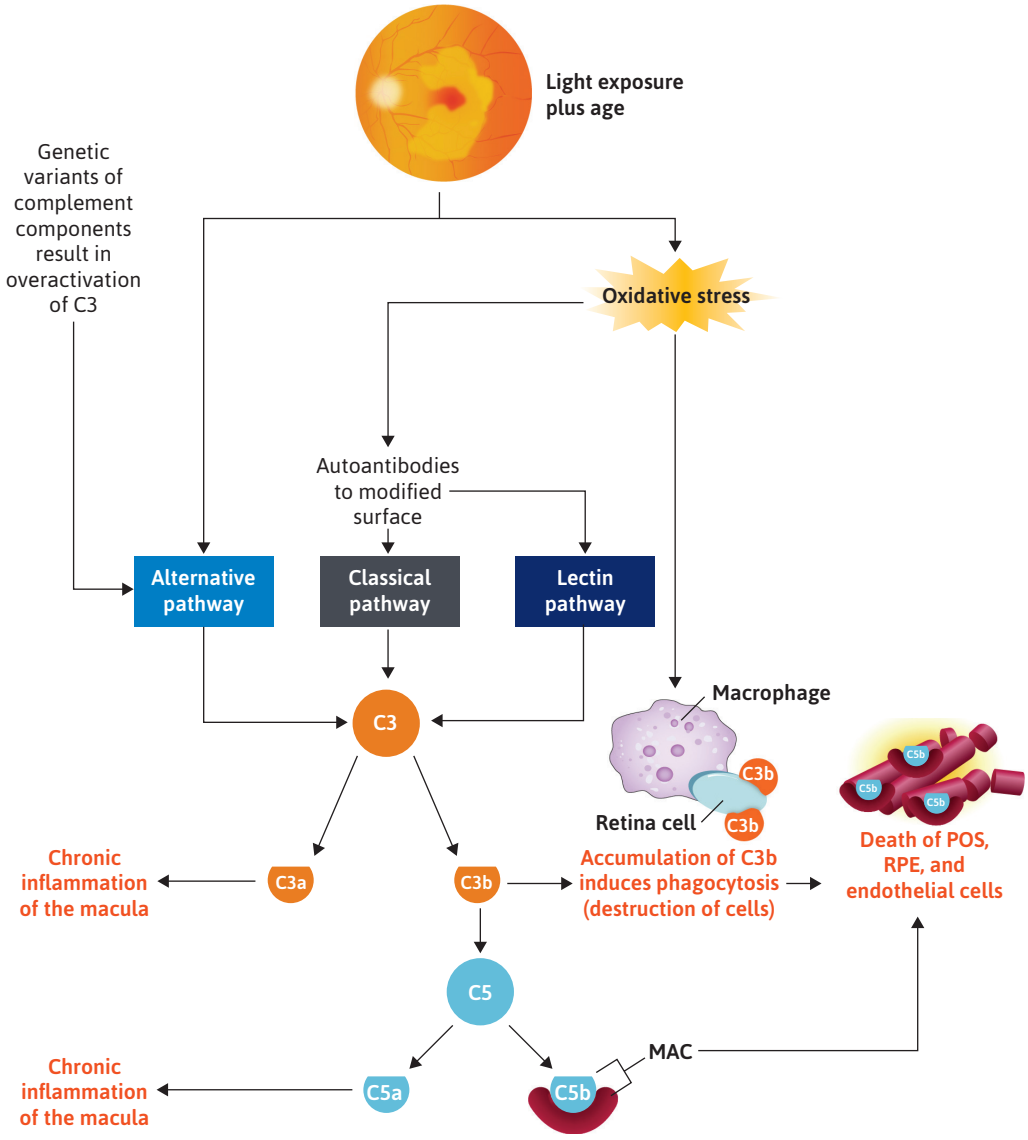
Role of Complement in GA

Genome-wide association studies have found genetic variants of factors of the complement pathway to be associated with increased risk of AMD. A genetic variant in the complement C3 gene was found to be associated with AMD, including GA.[15] Overactivation of the complement system is strongly associated with lesion development and progression in GA. In particular, it is associated with the loss of photoreceptors, RPE, and choriocapillaris.[4,16] Photoreceptors are specialized sensory cells that convert light into electrical impulse.[17] The outer segment of the photoreceptors is connected to the RPE, which is a single cell layer in the outer layers of the retina that plays a critical role in the maintenance and survival of the photoreceptor cells, in clearing cellular debris, and in regulating the integrity of the choroidal capillaries.[18,19] Choriocapillaris supplies blood to the outer layer of the retina and nourishes the retinal nerve cells.[18] When functioning normally, the complement system is an important part of the body's natural immune response. Under steady-state conditions, complement proteins are deployed to rapidly respond to microbes and stress signals. However, overactivation or loss of regulation of this host response can have detrimental consequences by perpetuating a vicious cycle of tissue injury and inflammation. Complement activity is found in both GA lesions and areas just outside the lesion. In areas outside the lesion, complement activation may accelerate cell damage, thereby increasing the risk of lesion growth.

In the complement system, the complement protein C3 plays a central role in driving the downstream damaging effects of complement overactivation and progression of GA for the following reasons[20] (Figure 1):

1. All of the 3 canonical complement activation pathways (classical, lectin, and alternative pathways) converge at C3, with convertase-mediated cleavage of C3 into C3a/C3b, which is associated with downstream effects, and C3b, which is associated with amplification of complement activation. Activation of both C3 and further downstream C5 is necessary to initiate the assembly of the membrane attack complex (MAC), which causes cell membrane destruction and, hence, cell death.
2. Overactivation of the complement system leads to excess phagocytosis, inflammation, and cell lysis (Figure 2)—all of which are thought to contribute to retinal cell death.
3. C3a and, further downstream, C5a activate and recruit inflammatory cells to the site of activation.

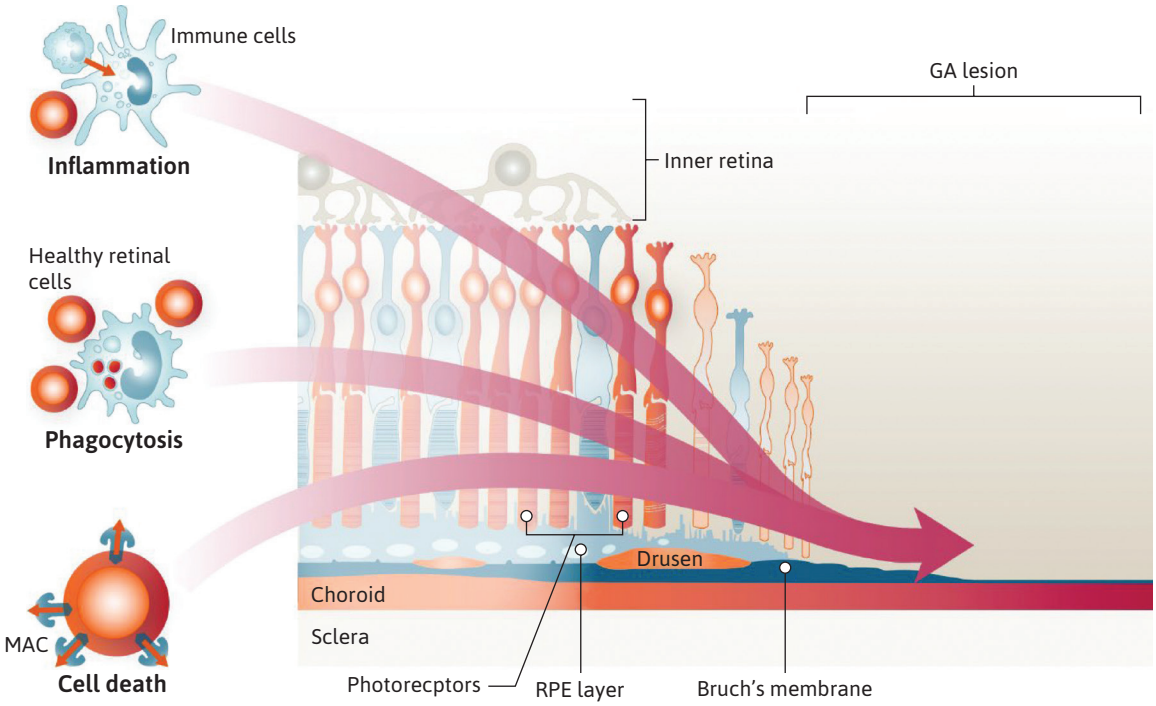
FIGURE 1 Role of C3 in Complement Overactivation and Progression of Geographic Atrophy



A schematic illustration of the complement system. Image does not reflect all proteins involved in the complement cascade.
MAC = membrane attack complex; POS = photoreceptor outer segment; RPE = retinal pigment epithelium.

The complement system is involved in drusen formation, and C3 and C5 fragments have been detected in drusen in histopathological probes of patients with AMD. Activation of the complement cascade results in cleavage of factor C5 into C5a and C5b fragments. The C5a fragment is an important inflammatory activator that is deposited in the drusen of patients with AMD. C5a recruits inflammatory cells and stimulates RPE cells to produce VEGF. The C5b fragment leads to the formation of MAC, which precipitates in Bruch's membrane and choriocapillaris, the degree of which is age and AMD dependent. The deposition of MAC in choriocapillaris and its presentation to choroidal endothelial cells trigger cell lysis, likely contributing to RPE atrophy in atrophic AMD and nAMD, respectively. Because of the complement cascade's role in the pathology of AMD, complement inhibition has been identified as a key

FIGURE 2 Proposed Role of the Complement Cascade in GA



Arrow points to GA lesion with missing photoreceptors and RPE. The proposed role of the complement cascade in GA shows how inflammation, phagocytosis, and cell death lead to the formation of GA. The schematic diagram shows the disappearance of the photoreceptors, RPE, and choriocapillaris, revealing the choroid underneath (which is unaffected).

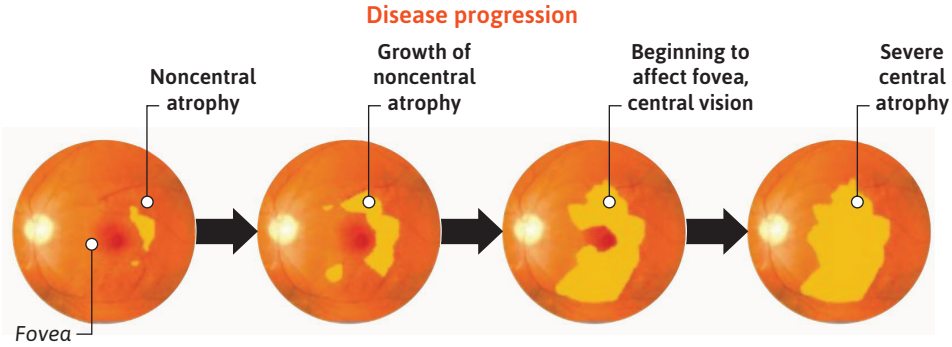
GA = geographic atrophy; MAC = membrane attack complex; RPE = retinal pigment epithelium.

candidate for therapeutic intervention.[4] Current mechanism and pathophysiology being targeted include complement factor C5 with the agent avacincaptad pegol/ARC1905 (Zimura; phase 3), which is a pegylated RNA aptamer that binds and inhibits C5[21,22] and cell therapy by transplanting RPE cells into the subretinal space to replace damaged RPE cells (phase 2a).[23] Pegcetacoplan, recently approved by the FDA for intravitreal injection for GA secondary to AMD, is a complement inhibitor that binds to complement protein C3 and its activation fragment C3b to regulate the cleavage of C3 and the generation of downstream effectors of complement activation.[9]

Signs and Symptoms

GA leads to scotomas, also known as visual field deficits or blind spots. GA encompasses the degeneration of the macula, which is the most central area of the retina and responsible for detailed central vision. The fovea, located in the center of the macula, contains a high density of cone photoreceptors and is responsible for central and color vision. However, even without the involvement of the fovea, lesions outside the fovea may cause visual disabilities in daily life, including reading and recognizing faces. The hallmark sign of GA—sharply demarcated atrophic lesions due to loss of photoreceptors, RPE, and choriocapillaris—which first appears in the outer retina, causes progressive visual impairment by expanding toward the fovea and eventually leading to irreversible vision loss (Figure 3).[4,5] These atrophic lesions in the outer retina, referred to as lesions without subfoveal involvement (also termed extrafoveal lesions), appear early in the disease and may cause vision loss early in the progression of the disease. Often, the fovea can be spared until later in the course of the disease, resulting in visual acuity that remains nearly normal. However, contrast sensitivity and ability to read may suffer. Once lesions encroach on the center point of the fovea with progressive disease, they are referred to as lesions with subfoveal involvement (also termed *foveal lesions*). With

FIGURE 3 Progression of Nonsubfoveal Atrophic Lesions to Subfoveal Lesions



subfoveal involvement, central vision is severely impaired and the patient experiences rapid loss of visual acuity function. Median time from nonsubfoveal to subfoveal involvement of GA ranges from 1.4 to 2.5 years.

Diagnosis

GA is not diagnosed by laboratory or genetic testing. Diagnosis of GA is made with the use of visual function tests to assess visual impairments and imaging tests to detect clinical features.

Impairments in visual function in patients with GA can be measured using the following methods[24]:

1. Reading charts may be used to measure visual acuity; however, these frequently provide poor information on actual retina function due to foveal sparing and parafoveal scotomas. Reading ability may be evaluated by the following 2 types of tests:
   - Best-corrected visual acuity (BCVA) is a standard vision assessment that employs the Snellen chart or the Early Treatment Diabetic Retinopathy Study chart to measure visual acuity. Visual acuity is measured by how many letters a patient can read at a distance. Depending on the degree of foveal sparing, patients may continue to be able to read individual letters and maintain BCVA.[5]
   - Reading speed, which can be quantified by the number of correctly read words over a prespecified period, provides information about how much of the visual field is sufficiently preserved to recognize entire words or sentences as opposed to individual letters. With progression of GA, reading speed declines.[5] Compared with patients with intermediate AMD, patients with GA and BCVA of 20/50 or more read significantly slower.[24] In a prospective natural history study of patients with GA, the median maximum reading rate decreased significantly from 110 words per minute (wpm) at baseline to 51 wpm at 2 years. In the comparison cohort of patients who had drusen only, the maximum reading rate decreased from 130 wpm at baseline to 117 wpm at 2 years, which was not significant.[25]
2. Other tests for assessing visual acuity include low-luminance visual acuity (LLVA) and low-luminance deficit. LLVA measures visual function in low-light and the process by which it is conducted is similar to that for BCVA but with one eye covered with a filter to reduce light exposure.[26] Low-luminance deficit is the difference between a patient's BCVA and LLVA scores and is predictive of subsequent vision loss and lesion enlargement in GA.[27]
3. The Amsler grid is used to examine impairments in a patient's central visual field and line detection. Healthy eyes see the graph lines sharply, in focus and with no distortion or blind spots. Patients with AMD may see the grid lines as wavy, blurred, or distorted, and where the visual field is impaired, the grid may appear to have "holes," dark areas, or scotomas.[28]
4. Microperimetry is an alternative to reading charts and may be used to measure retinal sensitivity in specific parts of the retina to identify functional and nonfunctional areas. This technique uses varying intensity of light to stimulate the macula in multiple locations to identify functional and nonfunctional areas; the result depends on the patient's ability to report recognition of the stimuli. With the use of an infrared camera, the fundus is monitored and the fixation point tracked, thus mapping the sensitivity of the visual field to the fundus photograph.[26]

Clinical features of GA are detected by using ophthalmoscopy and imaging in which it is defined by cell layer loss with sharply defined borders and by loss of RPE,

photoreceptors, and underlying choriocapillaris.[5] Common multimodal imaging techniques that enable visualization of the fundus and surrounding vasculature and are used to diagnose GA and define areas of atrophy include the following:

1. Color fundus photography (CFP): This is the historical standard for imaging GA and defines GA lesions as sharply demarcated areas of RPE hypopigmentation, with clearly visible underlying choroidal vessels, but CFP cannot be used to visualize characteristics of lesions associated with progressive GA.[5]
2. Optical coherence tomography (OCT): An imaging modality that identifies GA lesions by the loss of retinal layers through cross-sectional and/or en face images. It is emerging as a preferred modality to assess GA lesion features.[5]
3. Fundus autofluorescence (FAF): Use of short-wavelength light to visualize loss of RPE cells. Areas of GA lesions appear hypoautofluorescent (decreased autofluorescence) due to loss of RPE cells containing intrinsic fluorophores, such as lipofuscin. This is the primary modality for assessing GA lesion size and growth in clinical trials.[5]

The Classification of Atrophy Meetings group is an international group of experts who have coined the currently accepted classification system for GA based on imaging. They recommended that OCT should serve as the reference method for defining GA and its stages, given its ability to demonstrate different retinal layers in 3 dimensions, its wide availability, and the ease of OCT image acquisition.[29] They suggested that FAF be used for cases in which the diagnosis is unclear. A typical trajectory of diagnostic testing would entail BCVA followed by OCT. If the relevant equipment is available, then FAF would be acquired as needed, and in some cases, also CFP. GA and nAMD have unique sets of *International Classification of Diseases, Tenth Revision, Clinical Modification* codes[30]: GA lesions by laterality (right eye [H35.311X], left eye [H35.312X], bilateral [H35.313X]) and by foveal involvement (without subfoveal involvement [H35.31X3] and with subfoveal involvement [H35.31X4]).[30]

Disease Progression: Timeline and Measures of Progression

A retrospective cohort analysis in the United Kingdom of 1,901 patients with bilateral GA found that 66.7% of patients with bilateral GA who were eligible to drive at baseline progressed to vision loss that left them ineligible to drive, with a median time to progression of 1.6 years (IQR = 0.7-2.7 years). Furthermore, 16% of patients who were not blind at baseline (n = 1,693) became legally blind (median time to progression: 6.2 years; IQR = 3.3-8.5 years).[8]

In another UK retrospective cohort analysis using electronic medical records, GA in the fellow eye was associated with greater rate of progression to GA in the study eye (11.2 per 100 person-years) than choroidal neovascularization in the fellow eye (4.1 per 100 person-years) or early/intermediate AMD in both eyes (2.0 per 100 person-years).[2] Having GA in the fellow eye was also associated with higher risk of incident GA among US patients in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) study after 5 years of follow-up (adjusted hazard ratio: 2.31; 95% CI = 1.51-3.54).

The impact that lesion growth—an indicator of disease progression—has on functional vision is often not captured by BCVA, a standard vision assessment used to measure visual acuity. Many patients with a good BCVA score have difficulties with reading, indicating that BCVA assessments may underestimate functional deficits.[5] A pooled analysis of data from 2 phase 3 clinical trials of GA failed to find strong correlations between GA lesion size and a range of functional end points.[31] Reading speed can give information on the extent of the visual field and whether it is preserved enough to read entire words or sentences instead of individual letters.[5] Therefore, disease progression is best determined by monitoring anatomical progression using multimodal imaging approaches (as described above).

Heterogeneity of Lesions

Lesions associated with GA are heterogeneous with several different presentations.[5] Various characteristics of the lesions affect the rate of progression, which varies from patient to patient. Lesions will eventually expand and grow toward the fovea to coalesce with other lesions to cover the fovea and affect vision.[5]

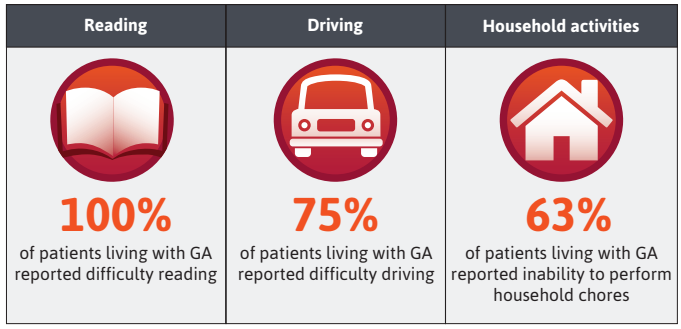
Lesion Characteristics That Influence Rate of Progression

Characteristics of GA lesions such as focality (unifocal vs multifocal lesions), location (subfoveal vs without subfoveal involvement), and lesion size affect the speed of disease progression.

1. Eyes with multifocal lesions have significantly higher mean (SE) GA growth rates than eyes with unifocal lesions (1.97 [0.1] mm^2/year vs 1.05 [0.2] mm^2/year; $P < 0.001$).[32]
2. In the Geographic Atrophy Progression study (N = 603), mean (SE) atrophy progression was observed to be significantly greater among eyes without subfoveal lesions compared with eyes with subfoveal lesions at month 6 (0.99 [0.1] mm^2 vs 0.65 [0.1] mm^2; $P = 0.011$) and at month 12 (2.05 [0.2] vs 1.28 [0.2]; $P = 0.001$).

Studies showed that larger baseline lesion size is associated with higher progression rates than smaller baseline lesion size.[33,34] In a study of 213 patients with GA, the GA growth rate was significantly correlated with mean GA perimeter ($r^2 = 0.66$; $P < 0.001$).[35] Furthermore, a literature review and meta-analysis showed that larger baseline GA area (in mm^2) was significantly correlated with larger mean GA growth rate (slope = 0.142 mm^2/year; $P < 0.001$). For every 1-mm^2 increase in mean baseline GA area, the mean GA growth rate increased by 0.14 (95% CI = 0.08-0.21) mm^2/year.[36] The presence of reticular pseudodrusen (subretinal drusenoid deposits above the RPE layer in contrast to drusen accumulating under the RPE[37]) is associated with a more rapid progression of GA.[38,39] In a clinical study, in the presence of reticular pseudodrusen the mean (95% CI) GA lesion growth rate was 0.32 (0.30-0.34) mm/year compared with 0.28 (0.25-0.31 mm/year; $P = 0.036$) without the presence of reticular pseudodrusen.[38]

FIGURE 4 Vision Loss Significantly Impacts Patients with Bilateral GA



Select activities of daily living measures shown. A cross-sectional ethnographic study (N=16) conducted to understand the impact of bilateral GA secondary to age-related macular degeneration on daily functioning by observing regular activities performed at home and through semistructured interviews.[40]

GA = geographic atrophy.

Impact of GA on Patients' Quality of Life

GA can profoundly affect patient functioning and interfere with activities of daily living. The consequences can be devastating in ways that are meaningful to patients. In an ethnographic study including 16 patients with GA, the most reported difficulties were reading (100%); driving (75%); watching movies, television, or theater (69%); recognizing faces (63%); and being unable to perform household chores (63%) (Figure 4).[40] Moreover, patients with GA feared worsening vision and of going blind and were frustrated with difficulties performing simple tasks, all of which impacted their emotional well-being.[40] Overall, quality of life in patients with GA, as assessed by the vision-specific 25-Item National Eye Institute Visual Function Questionnaire (with a higher score representing better functioning), has been shown to be worse than that in patients with early or intermediate AMD and nAMD. Analysis from a cross-sectional US study of 739 patients with AMD (294 with early/intermediate AMD, 115 GA, 168 nAMD, and 162 GA plus nAMD) showed that mean composite scores were highest among patients with early or intermediate AMD (89.9) and lowest for the groups with bilateral GA (71.3) and bilateral GA plus nAMD (68.5).[41] In a separate study, most patients with GA with a driver's license reported to mainly travel with a partner or friend, and the number one reason for giving up driving was eyesight. Driving is of particular concern, and inability to drive affects dependency.[42] As reported in the retrospective cohort analysis using an electronic medical record database, 67% of patients with bilateral GA who were eligible to drive at baseline progressed to vision loss that left them ineligible to drive in a median time of less than 2 years.[8]

Patients with GA are at high risk of developing clinical depression because of their inability to care for themselves and the impact of visual loss on life in general. Patients with unilateral blindness due to AMD are more often affected by depression than those with bilateral disease, possibly because of the fear of losing vision in the unaffected eye.[43] Moreover, patients with AMD have a high level of emotional stress that can be compared with patients with disabling chronic illness (eg, arthritis, acquired immunodeficiency syndrome, chronic obstructive pulmonary disease, and bone marrow transplant).[43] In addition to increased susceptibility to depression, fear, anxiety, and social isolation, patients with GA are more likely to fall.[43-45] In a prospective cohort study including Medicare patients, those with a code for atrophic AMD (N = 26,942) had an 11% increased risk (odds ratio: 1.11; 95% CI = 1.06 - 1.16; $P < 0.001$) of hip fractures compared with patients without a code for AMD (N = 1,013,748) over a 4-year follow-up period (1996 - 1999).[44]

Treatment Goals

There has been no treatment for GA until intravitreal pegcetacoplan was approved recently by the FDA for GA secondary to AMD. As the vision loss experienced by patients with GA is irreversible, the goal of a treatment is to slow progression of lesion growth.[5,6,9] Potential drugs currently in development

for the treatment of GA are focused on slowing lesion growth and long-term preservation of retinal tissue.[46,47]

Several complement inhibitors targeting various points along the complement pathway are being investigated in GA, including avacincaptad pegol (C5 inhibitor).[48]

Conclusions

GA is the advanced form of dry AMD characterized by atrophic lesions in the outer retina.[5] It is distinct from nAMD, which has different treatment goals, as it can be treated with anti-VEGF therapy; however, GA cannot be treated with anti-VEGF.[6] GA is a disease that is characterized by an irreversible progression leading to vision loss. Atrophic lesions can invade the fovea in less than 2 years from the point at which they form in the non-subfoveal retina. Therefore, early intervention preceding foveal involvement may slow lesion growth and preserve vision over the long term.[5]

The underlying pathology of GA lesion may be caused by the overactivation of the complement system. Genetic variants of complement factors are found to increase susceptibility to AMD. In the complement cascade, the complement protein C3 plays a central role in driving the downstream damaging effects of complement overactivation and progression of GA[20] and could therefore present a therapeutic target. NGM-621, an anti-C3 antibody, has failed to meet the primary endpoint in the CATALINA trial.[49] Additional therapeutic targets include mitochondrial dysfunction and oxidative stress; however, elamipretide, a mitochondria-targeting drug, has failed to meet its primary endpoint in the phase 2 ReCLAIM-2 trial.[47,50]

Until intravitreal pegcetacoplan, which is a complement C3 inhibitor, was recently approved by FDA for GA secondary to AMD, there has been a long-standing unmet need for therapies that slow the growth of lesions.[4,9]

DISCLOSURES

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