Ophthalmology ROUNDS

Volume 17, Issue 3

AS PRESENTED IN THE ROUNDS OF THE DEPARTMENT OF OPHTHALMOLOGY AND VISION SCIENCES, FACULTY OF MEDICINE, UNIVERSITY OF TORONTO

Novel Developments in the Management of Geographic Atrophy

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This issue of *Ophthalmology Rounds* focuses on geographic atrophy (GA), an advanced form of dry age-related macular degeneration (AMD). GA is characterized by progressive retinal pigment epithelium and photoreceptor atrophy and is regarded as a leading cause of irreversible vision loss. Historically managed with supportive care, the treatment landscape has recently shifted with the approval of pegcetacoplan and avacincaptad pegol by the United States Food and Drug Administration. These intravitreal injections target the complement cascade, demonstrating an ability to slow GA lesion growth. However, these agents have thus far demonstrated a lack of functional vision improvement and an increased risk of conversion to neovascular AMD, and there is limited access due to regulatory barriers. In this review, we discuss the multifactorial pathophysiology of GA, summarize the development and validation of existing complement inhibitor agents, and explore emerging therapies for this sight-threatening condition.

Introduction

Geographic atrophy (GA) is an advanced form of nonexudative (i.e., dry) age-related macular degeneration (AMD) that is defined by well-demarcated regions of atrophic retinal pigment epithelium (RPE) and loss of photoreceptors.[1,2] The global prevalence of GA varies across populations, with estimations ranging from 0.2%–3.5% in older adults.[3-5] Several risk factors for the development and progression of GA have been proposed, including soft indistinct drusen, reticular pseudodrusen (RPD), drusen located within 500 µm of the fovea, large drusen area, RPE changes (e.g., focal hyperpigmentation and depigmentation), increasing age, smoking, nutritional factors, diabetes, cardiovascular disease, ultraviolet light exposure, GA in the fellow eye, and specific gene variants.[6–11] Initial GA lesions are typically parafoveal, sparing the fovea before the lesions eventually expand to involve the subfoveal region.[12] Even while GA is extrafoveal, the disease may have an impact on visual function, manifesting as a paracentral visual field scotoma if sufficiently large. Subfoveal GA can significantly compromise quality of life, including activities involving near and distance vision, driving, social functioning, and mental health.[12,13]

Pathophysiology and Disease Mechanisms

In its severe stages, patients with AMD may experience one or both possible outcomes: 1) progression to GA, involving atrophy of the RPE, photoreceptors, and choriocapillaris, or 2) development of neovascular AMD (nAMD) **(Figure 1)**.[14] Importantly, these 2 outcomes are not mutually exclusive, but they warrant different treatment approaches.

The pathophysiology of GA is multifactorial. Oxidative damage contributes to the accumulation of intracellular debris, including lipofuscin, in RPE cells.[15] Lipofuscin accumulation may induce cell injury, dysregulate RPE function, and lead to extracellular deposits of lipid-rich drusen between the RPE and Bruch's membrane.[15] Abnormalities in the complement system are thought to drive drusen formation, which subsequently activates the complement system, forming a positive feedback loop as continued complement activation and inflammation lead to cellular damage and atrophy.[15] The eventual collapse or regression of drusen is often a precursor to GA, indicating the clearance of drusen deposits following the degeneration of the RPE.[16] Other precursor lesions include RPE hyperpigmentation or hypopigmentation, refractile deposits, pigment epithelial detachments, vitelliform lesions, and RPD.[17] Activation of the complement cascade can occur via the classical, lectin, and alternative pathways, which converge with the formation of C3 convertase, eventually leading to the assembly of membrane attack complexes that can lyse target cells.[18] The alternative pathway plays a major role in GA pathogenesis **(Figure 2)**.[14]

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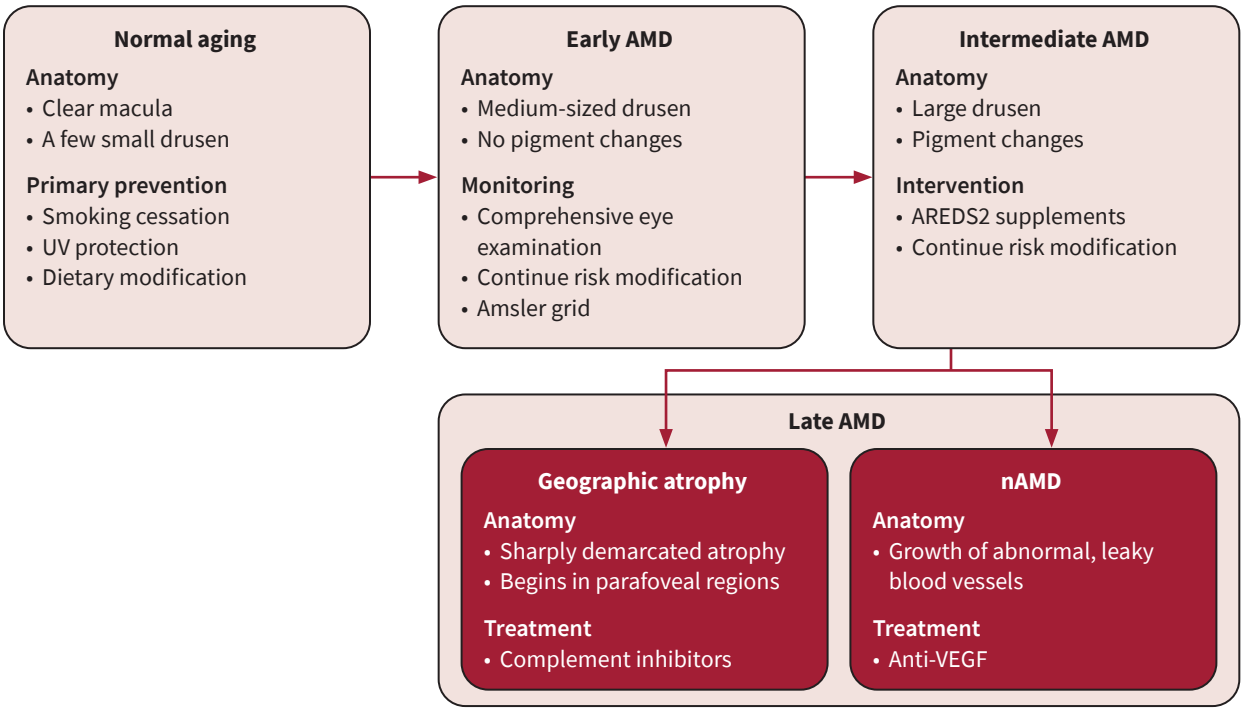
Figure 1. Progression of AMD with associated anatomical changes and clinical interventions.



AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; n, neovascular; UV, ultraviolet; VEGF, vascular endothelial growth factor

Serum complement activation products, including Bb (derived from complement factor B) and the anaphylatoxins C3a and C5a, are elevated in patients with GA.[19] Previous studies have found that elevated C3a/C3 and C5a/C5 ratios are strongly associated with progression to GA over nAMD.[20]

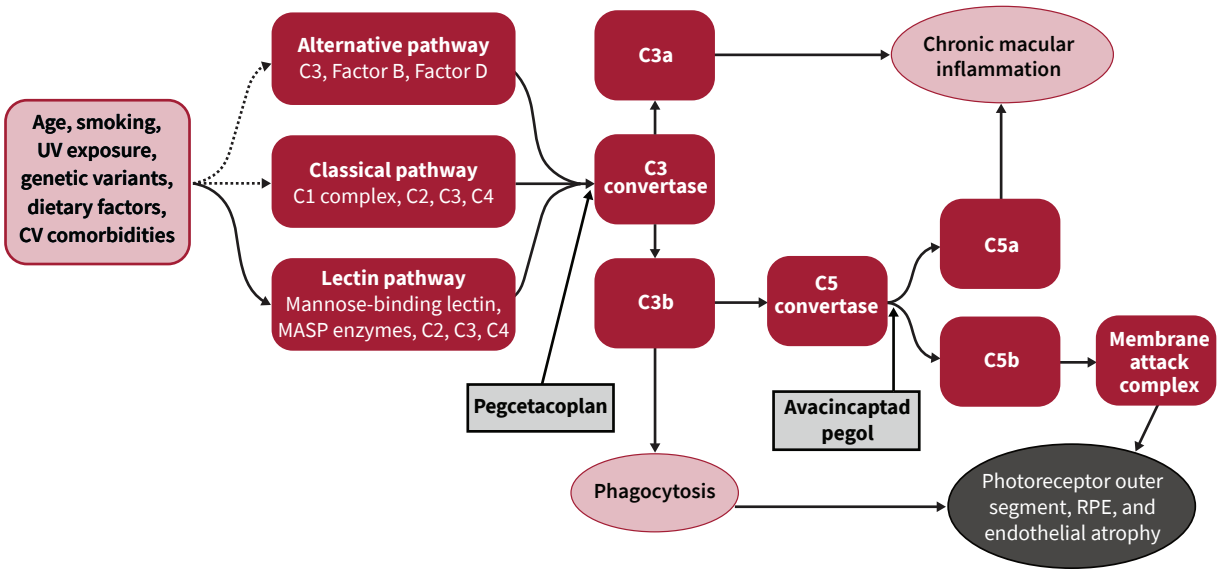
Other inflammatory pathways also contribute to GA pathogenesis. Activation of the nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 inflammasome leads to assembly of the multiprotein complex and activation of caspase-1, which promotes maturation and release of the proinflammatory cytokines interleukin-1β and interleukin-18 and induces pyroptotic cell death.[21] Although activation of the inflammasome has been associated with RPE cell death, the exact mechanism remains unclear.[22] The accumulation of ribonucleic acid, drusen components (e.g., C1q), and other complement components such as C3a and C5a have been implicated in inflammasome activation.[22]

Upregulation of mitochondrial dysfunction pathways has been identified in GA.[23] Accumulation of reactive oxygen species (ROS) can impair mitochondrial function in RPE cells, leading to increased inflammation that amplifies ROS production, creating a positive feedback loop.[24] This oxidative damage leads to RPE dysfunction and apoptosis, which precipitates photoreceptor degeneration.[24] Defective energy metabolism, mitophagy, and increased ROS production contribute to cellular stress, inflammation, and apoptosis in the RPE and outer retina.[25] The resulting RPE dysfunction, combined with complement activation, leads to degeneration of the choriocapillaris. The choriocapillaris, the primary vascular supply to the outer retina, classically degenerates in GA alongside RPE and photoreceptor loss.[26] Indeed, deficits in choriocapillaris flow have been associated with faster GA lesion growth and reduced central visual function.[27,28] The extent of choriocapillaris impairment often exceeds the boundaries of atrophy, allowing for its use in quantitative imaging as a marker of risk and progression.[29] Ultimately, the combination of chronic RPE dysfunction, oxidative stress, complement-mediated inflammation, and loss of support from the choriocapillaris leads to irreversible photoreceptor atrophy.

GA is also characterized by abnormal lipid metabolism. The accumulation of ceramides and decline in phospholipids signify significant disruption of lipid homeostasis.[30,31] Genes involved in lipid metabolism, including *ABCA1* and *GPX4*, have been identified as potential drug targets in AMD.[32] Impaired lipid transport, accumulation of lipoproteins, and dysregulated cholesterol efflux in the RPE all contribute to the production of drusen.[33]

The genetic variants that most strongly affect GA risk are related to the complement pathway, including *CFH*, *CFB*, *FHR1-FHR3*, and *C3*.[8,34] Several genes have been implicated in the risk for GA progression. The age-related maculopathy susceptibility 2 (*ARMS2*) and high-temperature requirement A serine peptidase 1 (*HTRA1*) gene risk alleles, particularly the single-nucleotide polymorphism rs10490924, have been associated with faster enlargement

Figure 2. Overview of the complement system in GA and the targets of existing complement inhibitors.



CV, cardiovascular; MASP, mannose-binding lectin-associated serine protease; RPE, retinal pigment epithelium

of GA lesions. The *ARMS2* and *HTRA1* genes are tightly linked. Patients with two risk alleles (TT) had the greatest rate of GA lesion enlargement (0.317 mm/year, 95% CI 0.279 to 0.355), followed by one allele (GT; 0.298, 95% CI 0.271 to 0.324) and no risk alleles (GG; 0.224, 95% CI 0.195 to 0.252, $P<0.0001$).[35] Increased enlargement was most pronounced in eyes with small lesions.[35] The exact function of the ARMS2 protein is unknown, although it may regulate mitochondrial homeostasis and the extracellular matrix.[36] Conversely, HTRA serine protease, coded by *HTRA1*, regulates cell growth, and overexpression has been linked to inflammation and neovascularization, particularly at the RPE-Bruch membrane interface.[37] The protein arginine methyltransferase 6 rs1184959 and lanosterol synthase rs2839127 loci have also been associated with disease progression.[38] The PRMT6 protein, which is involved in post-translational protein modification, contributes to normal retinal structure. PRMT6 is expressed more in the peripheral RPE and choroid than the central region, and dysregulation may affect GA lesion localization.[38] Finally, the LSS protein is an enzyme used for cholesterol synthesis and is necessary for normal retinal vasculature.[38] Together, these loci serve as potential targets for risk stratification and future treatments.

Imaging and Biomarkers in Diagnosis

Multimodal retinal imaging is important for the diagnosis and monitoring of GA. In recent years, studies harnessing machine learning models have confirmed and identified several important biomarkers of severity and progression. Optical coherence tomography (OCT) and fundus autofluorescence (FAF) are the most common modalities used in GA surveillance.[39,40] OCT provides high-resolution cross-sectional visualization of retinal layers and can reliably diagnose GA. Numerous terms established by the Classification of Atrophy Meetings program are now employed to capture the severity of possible GA lesions on OCT, including complete RPE and outer retinal atrophy (cRORA), incomplete RPE and outer retinal atrophy (iRORA), complete outer retinal atrophy (cORA), and incomplete outer retinal atrophy (iORA).[41] cRORA is defined as homogeneous choroidal hypertransmission and absence of the RPE band measuring ≥250 µm, accompanied by overlying outer retinal thinning and photoreceptor loss. iRORA is defined as a region of choroidal hypertransmission and corresponding attenuation or disruption of the RPE with overlying photoreceptor degeneration that does not meet the definition of cRORA. Despite their prognostic value, there are limitations to the detection of iRORA, including variations in OCT devices and difficulties in accurately measuring size to distinguish from cRORA when lesions span the border of adjacent scans.[42,43] OCT also allows for the detection of drusen, RPD, and hyperreflective foci, which have been identified as risk factors for GA onset and progression.[42,44-46] Loss of the ellipsoid zone and/or RPE, and thinning of the outer nuclear layer are also indicative of GA progression.[15,47,48]

FAF visualizes the autofluorescent properties of lipofuscin, an accumulated byproduct of photoreceptor damage.[39] Although lipofuscin accumulates with age, GA lesions lack lipofuscin due to RPE atrophy, appearing as hypofluorescent areas on FAF.[39] On colour fundus photography, drusen appear as yellowish-whitish deposits, whereas on FAF they may demonstrate decreased autofluorescence, correlating with outer retinal thinning.[49] RPD appear as interlacing networks of hypoautofluo-

rescent lesions, namely dots or ribbons, against a background with mildly reduced or iso-autofluorescence.[50,51] Vitelliform lesions typically show intense hyperautofluorescence in early stages, but become hypoautofluorescent as atrophy develops.[52]

Lifestyle Modifications

Several important modifiable risk factors should be targeted in patients with dry AMD, including GA. Smoking cessation is incredibly important among patients who are at risk for AMD and those who already have AMD.[15,53] A 40 pack-year smoking history was associated with >3 times greater odds of developing GA, and current smokers have a 3-fold increase in risk for AMD compared to patients who never smoked.[15,53] Further, some studies suggest that the increased risk can be partially reversed upon smoking cessation.[15] Dietary modifications, particularly adherence to a Mediterranean diet, have been associated with decreased progression to late AMD.[54] Increased physical activity may be associated with reduced incidence and slowed progression of AMD.[55]

Current Treatments

For patients with bilateral intermediate AMD or one eye with intermediate and the other with advanced AMD, the Age-Related Eye Disease Study (AREDS) and AREDS2 studies showed that oral micronutrient supplementation can reduce the progression of AMD.[56] A 2025 *post hoc* analysis of AREDS2 participants found that randomization to lutein and zeaxanthin reduced proximity-based progression of GA compared to controls (-34.3 µm/year; 95% confidence interval [CI] -60.8 to -7.8; *P*=0.011), although there was no significant difference in area-based progression.[57] This study provided the first large-scale evidence that use of AREDS2 vitamin supplementation impacted the extent to which GA grew towards the fovea. Importantly, AREDS2 supplementation is not a treatment that reverses established GA.

Beyond the preventive benefits of AREDS/AREDS2, there were until recently no evidence-based treatments to slow the progression of GA. In 2023, pegcetacoplan and avacincaptad pegol (ACP) were approved by the United States (US) Food and Drug Administration (FDA) for the treatment of GA secondary to AMD.[58] Both drugs target the complement cascade; pegcetacoplan targets complement component 3 (C3), and ACP targets C5.[58] The evidence to date suggests that the benefits of these treatments are largely anatomical and limited to slowing GA progression without being able to reverse GA. Longer-term follow-up may be required to demonstrate a preventive effect, with pivotal clinical trials only beginning to report data beyond 24 months.[59] As of August 2026, neither drug has been approved for use in patients with GA by Health Canada, although ACP is currently under review.[60,61]

ACP

The primary evidence in support of ACP is the GATHER1 and GATHER2 trials.[62,63] GATHER1 was a 2-part study that randomized 77 eyes 1:1:1 to ACP 1 mg, ACP 2 mg, or sham intravitreal injection and 209 eyes 1:2:2 to ACP 2 mg, 4 mg, and sham, all with monthly dosing.[62] In eyes receiving ACP 4 mg, the least-squares mean (LSM) GA lesion growth was -0.167 mm^2 (95% CI -0.273 to -0.062), representing a difference of -30.0% compared to sham, while the difference in LSM lesion growth was -28.1% (-0.168 mm^2; 95% CI -0.271 to -0.066) in eyes receiving ACP 2 mg compared to sham. Both ACP 2 mg and 4 mg showed numeric improvement in best-corrected visual acuity (BCVA) and low light VA compared to sham, although the results were not statistically significant. ACP was well tolerated, with most adverse events (AEs) relating to the injection procedure. There was 1 case of intraocular inflammation in the ACP 2 mg group (1.5%) and no cases of endophthalmitis. There was 1 severe ocular AE in each intervention group: optic ischemic neuropathy in ACP 2 mg (1.5%) and retinal detachment in ACP 4 mg (1.2%). New-onset nAMD was observed in 8 eyes (11.9%) in the ACP 2 mg group, 9 eyes (10.7%) in the ACP 4 mg group, and 2 eyes (1.8%) in the sham group. Choroidal neovascularization was identified in 4 eyes (4.8%) of the ACP 4 mg group and in 1 eye (0.9%) of the sham group.

GATHER2 randomized 448 eyes 1:1 to ACP 2 mg monthly or sham.[63] At 12 months, eyes receiving ACP 2 mg were re-randomized 1:1 to continue ACP 2 mg monthly or switch to ACP 2 mg every other month (EOM). The LSM difference in GA lesion growth in the ACP 2 mg monthly group vs sham was -0.724 mm^2 (-14%; 95% CI -1.315 to -0.133; *P*=0.017), and was -0.976 mm^2 (-19%; 95% CI -1.575 to -0.377; *P*=0.002) for ACP 2 mg EOM vs sham at 24 months. By 24 months, the difference in change in BCVA was -0.83 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (95% CI -3.79 to 2.12, *P*=0.58). ACP was generally well tolerated, although more cases of ocular treatment-emergent AEs were related to ACP in the study eye in the ACP 2 mg group (n=7; 3.1%) versus sham (n=2; 0.9%). Over 24 months, there was 1 event (0.4%) of intraocular inflammation in the treatment group and 1 (0.4%) confirmed event of endophthalmitis. There were 26 (11.6%) new-onset events of choroidal neovascularization in the ACP 2 mg group and 20 (9.0%) in the sham group.

Pegcetacoplan

The pivotal evidence for pegcetacoplan comes from the Phase III OAKS and DERBY trials, which randomized a combined 1258 eyes and analyzed 1211 (96.3%) in the modified intention-to-treat (mITT) population.[64] Participants were randomized 2:2:1:1 to receive 15 mg intravitreal injections of pegcetacoplan monthly, pegcetacoplan EOM, sham monthly, or sham EOM. Over 24 months, the

LSM change in lesion area vs sham was -0.82 mm^2 (-21%; 95% CI -1.11 to -0.54; *P*<0.0001) among eyes receiving monthly pegcetacoplan and -0.69 mm^2 (-17%; 95% CI -0.97 to -0.40; *P*<0.0001) among eyes receiving EOM pegcetacoplan. The greatest reduction occurred in parafoveal and perifoveal regions (monthly pegcetacoplan vs sham -26%; *P*<0.0001; EOM pegcetacoplan vs sham -22%; *P*<0.0001) rather than subfoveal regions (monthly pegcetacoplan vs sham -19%; *P*<0.0001; EOM pegcetacoplan vs sham -16%; *P*=0.0003). A *post hoc* analysis of GA OCT features found detectable differences in RPE loss and outer retinal atrophy as early as 3 months between pegcetacoplan and sham, which persisted every month until 24 months.[65] However, there were no significant differences between treated and sham groups in functional endpoints—change in VA, maximum reading speed, National Eye Institute Visual Functioning Questionnaire 25 distance activity score, and macular sensitivity—at 24 months.[64] Pegcetacoplan had a generally acceptable tolerability, although there were several notable AEs. New-onset nAMD was reported in a higher proportion of eyes receiving pegcetacoplan monthly (OAKS n=24 [11.3%], 25 events; DERBY n=27 [13.1%], 30 events) and EOM (OAKS n=16 [7.6%], 17 events; DERBY n=12 [5.8%], 12 events) vs sham (OAKS n=4 [1.9%], 4 events; DERBY n=9 [4.4%], 11 events). Intraocular inflammation was reported at a rate of 0.24% per injection at 24 months, with most cases classified as mild or moderate.[64] Infectious endophthalmitis rates per injection were 0.05% at 12 months and 0.03% at 24 months, which is consistent with other intravitreal injection therapies.[57,66] Serious treatment-emergent ocular AEs were low, with 5 (2.3%), 4 (1.9%), and 1 (0.5%) in OAKS and 4 (1.9%), 2 (1.0%), and 2 (1.0%) in DERBY eyes receiving pegcetacoplan monthly, pegcetacoplan EOM, and sham, respectively.[64] These included endophthalmitis (3 eyes [1.4%] in OAKS pegcetacoplan EOM and 2 eyes [0.9%] in OAKS pegcetacoplan monthly) and ischemic optic neuropathy (2 eyes [0.9%] in OAKS pegcetacoplan monthly and 1 eye [0.5%] in DERBY pegcetacoplan monthly). The GALE 12-month open-label extension to OAKS and DERBY provided data to 36 months of treatment with pegcetacoplan.[67] Efficacy aligned with the findings from OAKS and DERBY; i.e., increased reduction in overall GA lesion growth in the pegcetacoplan monthly (-25%, -1.49 mm^2) and EOM (-20%, -1.21 mm^2) versus sham, with increased reduction in nonsubfoveal regions.[67] Microperimetry analysis found an 18% reduction (*P*=0.0156) in the number of new scotomatous points in the pegcetacoplan monthly group versus sham, while the EOM group did not reach a statistically significant decrease (12%; *P*=0.1233).

A post-marketing report from the American Society of Retina Specialists Research and Safety in Therapeutics Committee confirmed retinal vasculitis in 14 eyes of 13 patients presenting within a median of 10.5 days (range 8–23) of pegcetacoplan initiation.[68] VA declined by >15 ETDRS letters in 8 eyes (57.1%), by >30 letters in 6 eyes (42.9%), and 2 eyes (14.3%) required enucleation. Overall, 12 eyes (85.7%) had vitritis, 6 eyes (42.9%) developed neovascularization, and all 11 cases of retinal vasculitis that could be graded involved the retinal veins.

Evidence synthesis

Pegcetacoplan and ACP have demonstrated statistically significant reductions in GA lesion growth compared to sham, although neither showed evidence of a significant improvement in visual function by 24 months. Pegcetacoplan appeared to be associated with a broader spectrum of ocular AEs than ACP, including increased rates of retinal vasculitis. A study using matching-adjusted indirect comparisons between OAKS, DERBY, and GATHER2 found that pegcetacoplan monthly had significantly less lesion growth than those receiving ACP monthly (-0.589 mm^2; -30%; 95% CI -1.164 to -0.015; *P*=0.04).[69] A numerically greater reduction in lesion size (-0.415 mm^2; -21%; 95% CI -1.130 to 0.300; *P*=0.25) was determined for pegcetacoplan EOM vs ACP monthly, suggesting that pegcetacoplan EOM may be more suitable to reduce treatment burden for patients and their caregivers. However, this analysis relied on a narrower sample size to balance baseline differences between trials, which may limit the generalizability of its findings to the broader population of patients with GA.

A real-world comparative observational study of pegcetacoplan (n=52) and ACP (n=60) found no significant differences between the interventions in any effectiveness outcomes over 12 months, including change in VA from baseline (pegcetacoplan -0.09 logarithm of the minimum angle of resolution (logMAR) [95% CI -0.13 to -0.05]; ACP -0.10 logMAR [95% CI -0.16 to -0.04]; *P*=0.57) and change in GA lesion size from baseline (*P*=0.61).[70] There was no significant difference in the incidence of macular neovascularization (pegcetacoplan 4 events [7.7%], ACP 7 events [11.7%]; *P*=0.66). There were no retinal vasculitis, vitritis, endophthalmitis, or vitreous hemorrhage events for any participant. Of note, the pegcetacoplan group had a much lower number of complement inhibition injections (5.96 versus ACP 9.05; *P*<0.01), which remained when including anti-vascular endothelial growth factor injections (pegcetacoplan 6.31 vs ACP 9.58; *P*<0.01). Ultimately, comparison of the safety profiles of these 2 drugs requires large-scale pharmacovigilance studies.

The disconnect of anatomic improvement without yet-apparent functional benefit raises questions about the clinical relevance of slowing GA without functional improvements. One hypothesis for this discrepancy is that the location of GA lesions may be more consequential than the size alone.[71] Long-term longitudinal data will be needed to determine if lesion growth inhibition ultimately leads to a significant preservation of VA.

Emerging Therapies

There are several therapies for GA in clinical development. Aside from targeting C3 and C5, other components of the complement system could serve as therapeutic targets to prevent the complement cascade that leads to cell

death in GA. Complement factors B, D, H, I, and the membrane attack complex have all been investigated as potential targets.[72] To date, most of these investigations have been unfruitful, including antisense oligonucleotides that target complement factors B (sefaxersen),[73] D (lampalizumab),[74] H (GEM103),[75] and I (GT005).[74] JNJ-81201887 is an investigational adeno-associated viral vector that delivers CD59 via intravitreal injection to inhibit membrane attack complex formation and reduce cell damage and death. After demonstrating a manageable safety profile in a Phase I trial, it is under investigation in a Phase II trial estimated to be completed by the end of 2026.[76,77] Pozelimab, a monoclonal antibody C5 inhibitor approved in the US for CD55-deficient protein-losing enteropathy, is being investigated as a subcutaneous injection in the Phase III SIENNA trial (estimated completion May 2032) and an intravitreal injection in the Phase I VIENNA study (estimated completion July 2028).[78,79]

Some neuroprotective therapies have also been investigated. ONL1204, an apoptosis inhibitor that targets the Fas receptor via intravitreal injection, may prevent retinal cell inflammation and death.[80] In a Phase Ib trial (N=28), ONL1204 demonstrated a favourable short-term safety profile and slower GA lesion growth over 6 months.[81] A Phase II study is underway, with completion estimated to be in 2028.[82]

Visual cycle modulators, which slow biochemical reactions in the eye, may be useful in GA by reducing the rate of toxic metabolite accumulation. Tinlarebant, a once-daily oral tablet that inhibits the retinol-binding protein 4–retinol complex, is being investigated for GA in the Phase III PHOENIX trial, with expected completion in August 2027.[83]

Photobiomodulation therapy may improve mitochondrial function and enhance cellular respiration by exposing the retina to low-intensity light. The LIGHTSITE III trial (N=148 eyes), investigating eyes with dry AMD without centre-involving GA, demonstrated a significant difference in BCVA between the Valeda Light Delivery System (VLDS) and sham (between-group difference 2.4 letters; 95% CI 0.1 to 4.7; *P*=0.02), and fewer patients receiving VLDS developed GA (1.1%, n=1) versus sham (10.0%, n=5; *P*=0.024).[84] The VLDS is approved for use in patients with dry AMD and without central-involving GA.[85]

By replacing damaged RPE cells, allogeneic stem-cell-based therapies delivered via subretinal surgical implantation may restore visual function. ASP7317, a human embryonic stem cell (hESC)-derived RPE cell therapy, is currently undergoing a Phase I trial.[86] OpRegen, a similar hESC-derived therapy, demonstrated meaningful disease stabilization and even some functional improvement in a Phase I/IIa clinical study; a Phase II trial is estimated to be completed by 2031.[87,88]

Conclusion

GA is a progressive manifestation of late AMD driven by complex interactions between complement dysregulation, inflammation, oxidative stress, and genetic susceptibility. Complement inhibitors, including pegcetacoplan and ACP, represent an important advance by slowing GA lesion growth, although significant functional benefits have not yet been demonstrated. Future therapies targeting complementary pathways, neuroprotection, visual cycle modulation, and retinal cell replacement may further improve management and ultimately help preserve meaningful visual function in patients with GA.

References

1. Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeren Campagne M. Geographic atrophy: Clinical features and potential therapeutic approaches. *Ophthalmology*. 2014;121(5):1079-1091.
2. 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.
3. Rim TH, Kawasaki R, Tham YC, et al. Prevalence and pattern of geographic atrophy in Asia: The Asian Eye Epidemiology Consortium. *Ophthalmology*. 2020;127(10):1371-1381.
4. Wilde C, Poostchi A, Hillman JG, MacNab HK, Vernon SA, Amoaku WM. Characteristics of geographic atrophy in an elderly UK population-The Bridlington eye assessment project (BEAP): A cross-sectional study (2002-2006). *Eye*. 2021;35(6):1697-1704.
5. Vujosevic S, Alovisi C, Chakravarthy U. Epidemiology of geographic atrophy and its precursor features of intermediate age-related macular degeneration. *Acta Ophthalmol (Copenh)*. 2023;101(8):839-856.
6. Eshtiaghi A, Issa M, Popovic MM, Muni RH, Kertes PJ. Geographic atrophy incidence and progression after intravitreal injections of anti-vascular endothelial growth factor agents for age-related macular degeneration: A meta-analysis. *Retina*. 2021;41(12):2424.
7. von der Emde L, Hou J, Mukherjee S, et al. Geographic atrophy multifocality in the Age-Related Eye Disease Study 2. *JAMA Ophthalmol*. 2025;143(12):1014-1023.
8. Caire J, Recalde S, Velazquez-Villoria A, et al. Growth of geographic atrophy on fundus autofluorescence and polymorphisms of CFH, CFB, C3, FHR1-3, and ARMS2 in age-related macular degeneration. *JAMA Ophthalmol*. 2014;132(5):528-534.
9. West SK, Rosenthal FS, Bressler NM, et al. Exposure to sunlight and other risk factors for age-related macular degeneration. *Arch Ophthalmol*. 1989;107(6):875-879.
10. Hogg RE, Woodside JV, Gilchrist SECM, et al. Cardiovascular disease and hypertension are strong risk factors for choroidal neovascularization. *Ophthalmology*. 2008;115(6):1046-1052.e2.
11. Chen X, Rong SS, Xu Q, et al. Diabetes mellitus and risk of age-related macular degeneration: A systematic review and meta-analysis. *PLOS ONE*. 2014;9(9):e108196.
12. Bakri SJ, Bektas M, Sharp D, Luo R, Sarda SP, Khan S. Geographic atrophy: Mechanism of disease, pathophysiology, and role of the complement system. *J Manag Care Spec Pharm*. 2023;29(5-a Suppl):S2-S11.
13. 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.
14. Fleckenstein M, Schmitz-Valckenberg S, Chakravarthy U. Age-related macular degeneration: A review. *JAMA*. 2024;331(2):147-157.
15. Guymer RH, Campbell TG. Age-related macular degeneration. *Lancet*. 2023;401(10386):1459-1472.
16. Spaide RF. Pathways to geographic atrophy in nonneovascular age-related macular degeneration. *Retina*. 2024;44(10):1655.
17. Klein ML, Ferris FL, Armstrong J, et al. Retinal precursors and the development of geographic atrophy in age-related macular degeneration. *Ophthalmology*. 2008;115(6):1026-1031.
18. Sarma JV, Ward PA. The complement system. *Cell Tissue Res*. 2011; 343(1):227-235.
19. Reynolds R, Hartnett ME, Atkinson JP, Giclas PC, Rosner B, Seddon JM. Plasma complement components and activation fragments: Associations with age-related macular degeneration genotypes and phenotypes. *Invest Ophthalmol Vis Sci*. 2009;50(12):5818-5827.
20. Lynch AM, Grove NC, Wagner BD, et al. Dynamic risk of systemic complement activation with time to progression to advanced age-related macular degeneration. *JAMA Ophthalmol*. 2025;143(8):634-642.

21. Tseng WA, Thein T, Kinnunen K, et al. NLRP3 inflammasome activation in retinal pigment epithelial cells by lysosomal destabilization: Implications for age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2013;54(1):110-120.
22. Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C. The pathophysiology of geographic atrophy secondary to age-related macular degeneration and the complement pathway as a therapeutic target. *Retina*. 2017;37(5):819.
23. Senabouth A, Daniszewski M, Lidgerwood GE, et al. Transcriptomic and proteomic retinal pigment epithelium signatures of age-related macular degeneration. *Nat Commun*. 2022;13(1):4233.
24. Ochoa Hernández ME, Lewis-Luján LM, Burboa Zazueta MG, et al. Role of oxidative stress and inflammation in age related macular degeneration: Insights into the retinal pigment epithelium (rpe). *Int J Mol Sci*. 2025;26(8):3463.
25. Kaarniranta K, Uusitalo H, Blasiak J, et al. Mechanisms of mitochondrial dysfunction and their impact on age-related macular degeneration. *Prog Retin Eye Res*. 2020;79:100858.
26. Sohn EH, Flamme-Wiese MJ, Whitmore SS, et al. Choriocapillaris degeneration in geographic atrophy. *Am J Pathol*. 2019;189(7):1473-1480.
27. Rinella NT, Zhou H, Wong J, et al. Correlation between localized choriocapillaris perfusion and macular function in eyes with geographic atrophy. *Am J Ophthalmol*. 2022;234:174-182.
28. You QS, Camino A, Wang J, et al. Geographic atrophy progression is associated with choriocapillaris flow deficits measured with optical coherence tomographic angiography. *Invest Ophthalmol Vis Sci*. 2021;62(15):28.
29. Sacconi R, Corbelli E, Borrelli E, et al. Choriocapillaris flow impairment could predict the enlargement of geographic atrophy lesion. *Br J Ophthalmol*. 2021;105(1):97-102.
30. Pujol-Lereis LM, Liebisch G, Schick T, et al. Evaluation of serum sphingolipids and the influence of genetic risk factors in age-related macular degeneration. *PLOS ONE*. 2018;13(8):e0200739.
31. Álvarez-Barrios A, Álvarez L, Sáenz de Santa María P, et al. Dysregulated lipid metabolism in a retinal pigment epithelial cell model and serum of patients with age-related macular degeneration. *BMC Biol*. 2025;23(1):96.
32. Fritsche LG, Igl W, Bailey JNC, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat Genet*. 2016;48(2):134-143.
33. Zhou S, Taskintuna K, Hum J, et al. PGC-1αrepression dysregulates lipid metabolism and induces lipid droplet accumulation in the retinal pigment epithelium. *Cell Death Dis*. 2024;15(6):385.
34. Scholl HPN, Fleckenstein M, Fritsche LG, et al. CFH, C3 and ARMS2 are significant risk loci for susceptibility but not for disease progression of geographic atrophy due to AMD. *PloS One*. 2009;4(10):e7418.
35. Agrón E, Domalpally A, Cukras CA, Chew EY, Keenan TDL. Critical dependence on area in relationship between ARMS2/HTRA1 genotype and faster geographic atrophy enlargement: AREDS2 Report 33. *Ophthalmology*. 2024;131(2):208-218.
36. Merle DA, Sen M, Armento A, et al. 10q26 – The enigma in age-related macular degeneration. *Prog Retin Eye Res*. 2023;96:101154.
37. Katschke KJ, Truong T, Pham V, et al. HTRA1-dependent proteolysis induces age-related retinal degeneration and exacerbates choroidal neovascularization. *Dis Model Mech*. 2025;18(10):dmm052253.
38. Grassmann F, Harsch S, Brandl C, et al. Assessment of novel genome-wide significant gene loci and lesion growth in geographic atrophy secondary to age-related macular degeneration. *JAMA Ophthalmol*. 2019;137(8):867-876.
39. Regillo CD, Nijm LM, Shechtman DL, et al. Considerations for the identification and management of geographic atrophy: Recommendations from an expert panel. *Clin Ophthalmol Auckl NZ*. 2024;18(10):325-335.
40. Mai J, Reiter GS, Riedl S, et al. Quantitative comparison of automated OCT and conventional FAF-based geographic atrophy measurements in the phase 3 OAKS/DERBY trials. *Sci Rep*. 2024;14(1):20531.
41. Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: Classification of atrophy report 3. *Ophthalmology*. 2018;125(4):537-548.
42. Vallino V, Berni A, Coletto A, et al. Structural OCT and OCT angiography biomarkers associated with the development and progression of geographic atrophy in AMD. *Graefes Arch Clin Exp Ophthalmol*. 2024;262(11):3421-3436.
43. Corvi F, Corradetti G, Nittala MG, et al. Comparison of Spectralis and Cirrus optical coherence tomography for the detection of incomplete and complete retinal pigment epithelium and outer retinal atrophy. *Retina*. 2021;41(9):1851.
44. Zhou Q, Daniel E, Maguire MG, et al. Pseudodrusen and incidence of late age-related macular degeneration in fellow eyes in the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2016;123(7):1530-1540.
45. Querques G, Querques L, Martinelli D, et al. Pathologic insights from integrated imaging of reticular pseudodrusen in age-related macular degeneration. *Retina*. 2011;31(3):518.
46. Bui PTA, Reiter GS, Fabianska M, et al. Fundus autofluorescence and optical coherence tomography biomarkers associated with the progression of geographic atrophy secondary to age-related macular degeneration. *Eye*. 2022;36(10):2013-2019.
47. Birner K, Reiter GS, Steiner I, et al. Structure-function correlation of deep-learning quantified ellipsoid zone and retinal pigment epithelium loss and microperimetry in geographic atrophy. *Invest Ophthalmol Vis Sci*. 2025;66(3):26.
48. Pfau M, von der Emde L, de Sisternes L, et al. Progression of photoreceptor degeneration in geographic atrophy secondary to age-related macular degeneration. *JAMA Ophthalmol*. 2020;138(10):1026-1034.
49. Göbel AP, Fleckenstein M, Heeren TFC, Holz FG, Schmitz-Valckenberg S. In-vivo mapping of drusen by fundus autofluorescence and spectral-domain optical coherence tomography imaging. *Graefes Arch Clin Exp Ophthalmol*. 2016;254(1):59-67.
50. Paavo M, Lee W, Merriam J, et al. Intraretinal correlates of reticular pseudodrusen revealed by autofluorescence and en face OCT. *Invest Ophthalmol Vis Sci*. 2017;58(11):4769-4777.
51. Sohrab MA, Smith RT, Salehi-Had H, Sadda SR, Fawzi AA. Image registration and multimodal imaging of reticular pseudodrusen. *Invest Ophthalmol Vis Sci*. 2011;52(8):5743-5748.
52. Schmitz-Valckenberg S, Holz FG, Bird AC, Spaide RF. Fundus autofluorescence imaging: Review and perspectives. *Retina*. 2008;28(3):385.
53. Khan JC, Thurlby DA, Shahid H, et al. 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 neovascularisation. *Br J Ophthalmol*. 2006;90(1):75-80.
54. Pameijer EM, Heus P, Damen JAA, et al. What did we learn in 35 years of research on nutrition and supplements for age-related macular degeneration: A systematic review. *Acta Ophthalmol (Copenh)*. 2022;100(8):e1541-e1552.
55. Mauschitz MM, Schmitz MT, Verzijden T, et al. Physical activity, incidence, and progression of age-related macular degeneration: A multicohort study. *Am J Ophthalmol*. 2022;236:99-106.
56. Apte RS. Age-related macular degeneration. *N Engl J Med*. 2021; 385(6):539-547.
57. Keenan TDL, Agrón E, Keane PA, Domalpally A, Chew EY. Oral antioxidant and lutein/zeaxanthin supplements slow geographic atrophy progression to the fovea in age-related macular degeneration. *Ophthalmology*. 2025;132(1):14-29.
58. Nissen AHK, Torp TL, Vergmann AS. Clinical outcomes of treatment of geographic atrophy: A narrative review. *Ophthalmol Ther*. 2025; 14(6):1173-1181.
59. Dinah C, Enoch J, Ghulakhszian A, et al. Patient-reported importance of functional benefit in geographic atrophy. *JAMA Ophthalmol*. 2025;143(11):916-924.
60. CDA-AMC. Avacincaptad pegol. Available at: https://www.cda-amc.ca/avacincaptad-pegol. Accessed on February 15, 2026.
61. Health Canada. Summary of cancellation for Syfovre (pegcetacoplan). Available at: https://dhpp.hpfb-dgpsa.ca/review-documents/resource/RDS1742305638383. Accessed on February 15, 2026.
62. Patel SS, Lally DR, Hsu J, et al. Avacincaptad pegol for geographic atrophy secondary to age-related macular degeneration: 18-month findings from the GATHER1 trial. *Eye*. 2023;37(17):3551-3557.
63. Khanani AM, Danzig CJ, Heier JS, et al. Avacincaptad pegol for geographic atrophy secondary to age-related macular degeneration: Two-year efficacy and safety results from the GATHER2 phase 3 trial. *Ophthalmology*. 2026;133(4):451-465.
64. Heier JS, Lad EM, Holz FG, et al. Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): Two multicentre, randomised, double-masked, sham-controlled, phase 3 trials. *Lancet*. 2023;402(10411):1434-1448.

65. Fu DJ, Bagga P, Naik G, et al. Pegcetacoplan treatment and consensus features of geographic atrophy over 24 months. *JAMA Ophthalmol*. 2024;142(6):548-558.
66. Daien V, Nguyen V, Essex RW, et al. Incidence and outcomes of infectious and noninfectious endophthalmitis after intravitreal injections for age-related macular degeneration. *Ophthalmology*. 2018;125(1):66-74.
67. Wykoff CC, Holz FG, Chiang A, et al. Pegcetacoplan treatment for geographic atrophy in age-related macular degeneration over 36 months: Data from OAKS, DERBY, and GALE. *Am J Ophthalmol*. 2025;276:350-364.
68. Witkin AJ, Jaffe GJ, Srivastava SK, Davis JL, Kim JE. Retinal vasculitis after intravitreal pegcetacoplan: Report from the ASRS Research and Safety In Therapeutics (ReST) Committee. *J Vitreoretin Dis*. 2024;8(1):9-20.
69. Hahn P, Eichenbaum D, Dhoot DS, et al. Efficacy of intravitreal pegcetacoplan vs avacincaptad pegol in patients with geographic atrophy. *J Vitreoretin Dis*. Published online October 17, 2025:24741264251379842.
70. Rush RB, Klein W, Reinauer RM. Real-world outcomes with complement inhibitors for geographic atrophy: A comparative study of pegcetacoplan versus avacincaptad pegol. *Clin Ophthalmol Auckl NZ*. 2025;19:1167-1174.
71. Csaky KG, Miller JML, Martin DF, Johnson MW. Drug approval for the treatment of geographic atrophy: How we got here and where we need to go. *Am J Ophthalmol*. 2024;263:231-239.
72. Tzoumas N, Riding G, Williams MA, Steel DH. Complement inhibitors for age-related macular degeneration. *Cochrane Database Syst Rev*. 2023;2023(6):CD009300.
73. Taylor NP. Ionis axes eye disease from targets of roche-partnered prospect after data disappoint | fierce biotech. August 1, 2024. Available at: https://www.fiercebiotech.com/biotech/ionis-axes-eye-disease-targets-roche-partnered-prospect-after-data-disappoint. Accessed on February 20, 2026.
74. Halawa OA, Lin JB, Miller JW, Vavvas DG. A review of completed and ongoing complement inhibitor trials for geographic atrophy secondary to age-related macular degeneration. *J Clin Med*. 2021;10(12):2580.
75. Gemini Therapeutics, Inc. A multicenter, open-label, multiple dose study in patients with geographic atrophy secondary to dry age-related macular degeneration to evaluate the safety, tolerability, pharmacodynamics, and immunogenicity of repeat intravitreal injections of GEM103. Available at: https://clinicaltrials.gov/study/NCT04643886. Accessed on February 20, 2026.
76. Janssen Research & Development, LLC. A phase 2b, randomized, double-masked, multicenter, dose-ranging, sham-controlled clinical trial to evaluate intravitreal JNJ-81201887 (AAVCAGsCD59) compared to sham procedure for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Available at: https://clinicaltrials.gov/study/NCT05811351. Accessed on February 20, 2026.
77. Heier JS, Cohen MN, Chao DL, et al. Phase 1 study of JNJ-81201887 gene therapy in geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2024;131(12):1377-1388.
78. Regeneron Pharmaceuticals. A multicenter, randomized, double-masked, placebo-controlled phase 3 study of the efficacy, safety, and tolerability of subcutaneously administered pozelimab in combination with cemdisiran or cemdisiran alone in participants with geographic atrophy secondary to age-related macular degeneration. Available at: https://clinicaltrials.gov/study/NCT06541704. Accessed on March 5, 2026.
79. Regeneron Pharmaceuticals. A phase 1 dose-escalation and repeated-dose study of the safety and tolerability of intravitreal pozelimab in participants with geographic atrophy. Available at: https://clinicaltrials.gov/study/NCT07230834. Accessed on March 5, 2026.
80. Kocab AJ, Cano M, Bacellar-Galdino M, et al. In vivo characterization of ONL1204, a small peptide inhibitor of the Fas receptor, as a potential neuroprotective therapy for geographic atrophy and dry age-related macular degeneration. *Biomedicines*. 2025;13(9):2052.
81. Kleinman DM, Wykoff CC, Borkar DS, et al. ONL1204 for the treatment of geographic atrophy: Phase Ib study evaluating safety, tolerability, and efficacy. *Ophthalmol Sci*. 2026;6(1):100954.
82. ONL Therapeutics. A phase 2 multicenter, randomized, double-masked, sham-controlled, reference-arm study to evaluate efficacy and safety of ONL1204 in patients with geographic atrophy (GA) associated with age-related macular degeneration (AMD). Available at: https://clinicaltrials.gov/study/NCT06659445. Accessed on February 20, 2026.
83. Belite Bio, Inc. Phase 3, multicenter, randomized, double-masked, placebo-controlled study of tinlarebant to explore safety and efficacy in the treatment of geographic atrophy (the PHOENIX Study). Available at: https://clinicaltrials.gov/study/NCT05949593. Accessed on March 5, 2026.
84. Boyer D, Hu A, Warrow D, et al. LIGHTSITE III: 13-month efficacy and safety evaluation of multiwavelength photobiomodulation in nonexudative (dry) age-related macular degeneration using the LumiThera Valeda light delivery system. *Retina*. 2024;44(3):487.
85. Russell MW, Rachitskaya AV. Photobiomodulation therapy for management of retinal diseases. *Curr Ophthalmol Rep*. 2025;13(1):13.
86. Astellas Institute for Regenerative Medicine. A phase 1b, multicenter, dose escalation, evaluation of safety and tolerability of ASP7317 for geographic atrophy secondary to age-related macular degeneration. Available at: https://clinicaltrials.gov/study/NCT03178149. Accessed on February 20, 2026.
87. Ho AC, Banin E, Barak A, et al. Safety and efficacy of a phase 1/2a clinical trial of transplanted allogeneic retinal pigmented epithelium (RPE, OpRegen) cells in advanced dry age-related macular degeneration (AMD). *Invest Ophthalmol Vis Sci*. 2022;63(7):1862-1862.
88. Genentech, Inc. A phase IIa, multicenter, open-label, single-arm study to optimize subretinal surgical delivery and to evaluate safety and activity of OpRegen in patients with geographic atrophy secondary to age-related macular degeneration. Available at: https://clinicaltrials.gov/study/NCT05626114. Accessed on February 20, 2026.

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Conflicts of Interest: Dr. Popovic reports being a consultant to or a member of an advisory board for Astellas, Bayer, Roche, and Sandoz, as well as financial support (to institution) from Bayer, Fighting Blindness Canada, and PSI Foundation. Mr. Gou and Dr. Tao stated that they have no disclosures to report in association with the contents of this issue.

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