# Current Treatments and Future Perspectives in Geographic Atrophy

# Tratamentos Atuais e Perspectivas Futuras na Atrofia Geográfica

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## ABSTRACT

Geographic atrophy (GA) secondary to age-related macular degeneration (AMD) is a progressive retinal degenerative disease and a major cause of irreversible vision loss in older individuals. No curative therapy is currently approved. This narrative review summarizes current and emerging therapeutic strategies for GA.

The complement system has emerged as a key therapeutic target, leading to the first approved pharmacological interventions for GA. Complement inhibitors, namely pegcetacoplan (C3 inhibitor) and avacincaptad pegol (C5 inhibitor), approved by the FDA in 2023, have demonstrated consistent reductions in GA lesion growth across phase 2 and phase 3 clinical trials. Although these therapies provide meaningful structural preservation, functional benefits remain modest, and treatment has been associated with an increased risk of conversion to neovascular AMD, highlighting the need for careful patient selection and monitoring.

Nutritional supplementation, particularly antioxidant formulations and lutein/zeaxanthin, has shown limited but measurable benefits in slowing disease progression, while photobiomodulation and emerging gene- and cell-based therapies appear promising strategies for retinal preservation and regeneration.

Despite recent advances, GA continues to be a debilitating condition with a significant impact on patients' quality of life. Current therapies offer partial benefits and do not halt or reverse retinal degeneration. Ongoing research aimed at optimizing treatment timing, combination strategies, and regenerative approaches is essential to improve long-term visual outcomes and address the substantial unmet needs associated with GA.

**KEYWORDS:** Geographic Atrophy/drug therapy; Geographic Atrophy/therapy; Macular Degeneration/complications.

## RESUMO

A atrofia geográfica (AG) secundária à degenerescência macular da idade (DMI) é uma doença degenerativa da retina e uma das principais causas de perda irreversível de visão em idosos. Atualmente, não existe qualquer terapêutica curativa aprovada. Esta revisão narrativa resume as

estratégias terapêuticas atuais e emergentes para a atrofia geográfica.

O sistema do complemento emergiu como um alvo terapêutico central, conduzindo ao desenvolvimento das primeiras terapêuticas farmacológicas aprovadas para a AG. Os inibidores do complemento, nomeadamente o pegcetacoplan (inibidor do C3) e o avacincaptad pegol (inibidor do C5), aprovados pela FDA em 2023, demonstraram reduções consistentes do crescimento das lesões de AG em ensaios clínicos de fase 2 e 3. Apesar da preservação estrutural alcançada, os benefícios funcionais permanecem modestos e foi observado um aumento do risco de conversão para DMI neovascular, sublinhando a necessidade de uma seleção criteriosa dos doentes e de uma monitorização rigorosa.

A suplementação nutricional, particularmente com formulações antioxidantes e luteína/zeaxantina, demonstrou benefícios limitados, mas mensuráveis, na desaceleração da progressão da doença, enquanto a fotobiomodulação e tratamentos emergentes baseados em terapia génica e com células estaminais se apresentam como estratégias promissoras para a preservação e regeneração da retina.

Apesar dos avanços recentes, a AG continua a ser uma condição debilitante, com impacto significativo na qualidade de vida dos doentes. As terapêuticas atualmente disponíveis oferecem benefícios limitados, não sendo capazes de interromper nem reverter a degeneração da retina. A investigação contínua, focada na otimização do *timing* terapêutico, estratégias combinadas e abordagens regenerativas, é essencial para melhorar os resultados visuais a longo prazo e responder às necessidades terapêuticas associadas à AG.

**PALAVRAS-CHAVE:** Degenerescência Macular/complicações; Atrofia Geográfica/tratamento; Atrofia Geográfica/tratamento farmacológico.

## INTRODUCTION

Age-related macular degeneration (AMD) is a progressive and chronic retinal neurodegenerative disease that primarily affects the macula.[1] It is the most common cause of irreversible vision loss in individuals over the age of 65 in industrialized countries and accounts for approximately 8% of blindness globally.[2,3]

Advanced age is the predominant risk factor for the development of AMD. However, family history, cigarette smoking, increased body mass index, hypertension, hyperlipidemia and specific genetic variants also appear to increase the risk for AMD.[1,4]

The etiology and pathophysiology of AMD are not fully understood, but key mechanisms include defects in autophagy, proteolysis, and lipid homeostasis, as well as altered responses to oxidative stress and mitochondrial dysfunction in the retinal pigment epithelium (RPE), a monolayer of cells critical for maintaining retinal homeostasis.[3-5] These changes contribute to the accumulation of lipid-rich yellow extracellular deposits known as drusen, which form beneath the RPE and disrupt its function, leading to photoreceptor degeneration.[1,3,4] Additionally, alterations in the extracellular matrix metalloproteinase system and chronic inflammation, with significant involvement of the complement system, further drive disease progression. Aging of the choroidal microvasculature also plays a critical role, contributing to vascular instability and retinal damage.[5]

The clinical staging of AMD is primarily based on the size of drusen, as identified through color fundus photography.[6] It exists in two main forms: dry (atrophic) and wet (neovascular). Dry AMD, which accounts for approximately 80%-85% of cases, progresses more slowly and includes early, intermediate, and late stages, the latter known as geographic atrophy (GA), characterized by well-defined, map-like lesions in the macula.[1,4,6] Wet AMD, although less common, accounts for the majority of cases of severe vision loss due to abnormal subretinal vessels.[1,6] While the underlying mechanisms are not fully understood, VEGF-driven angiogenesis and genetic factors appear to predispose certain individuals to develop the neovascular form rather than GA.[3,7]

Although early and intermediate forms of dry AMD are often asymptomatic or mildly symptomatic, late-stage AMD, especially GA, significantly impacts visual function. Patients frequently report central scotomas and distorted vision.[2] In advanced stages, central vision may be severely impaired, compromising the ability to read, drive and recognize faces, leaving only peripheral vision quite preserved.[3]

Currently, the therapeutic landscape offers effective treatment for wet AMD, primarily through intravitreal anti-VEGF agents. These drugs target vascular endothelial growth factor (VEGF), suppressing abnormal blood vessel formation and slowing disease progression.[3]

However, dry AMD lacks an approved curative therapy. The complexity of AMD pathogenesis contributes to the absence of fully effective therapeutic options. It is also presumed that, like in other neurodegenerative diseases, by the time treatment is usually initiated, irreversible loss of photoreceptor cells has already occurred, making functional recovery extremely difficult.[2]

At present, only two drugs are approved by the U.S.

Food and Drug Administration (FDA) for the treatment of GA secondary to AMD: pegcetacoplan, approved in February 2023, and avacincaptad pegol, approved in August 2023. However, neither drug has yet been approved by the European Medicines Agency (EMA) for the treatment of GA.

Beyond visual impairment, AMD profoundly affects patients' quality of life, often exacerbating age-related comorbidities in the elderly. Additionally, the condition imposes a significant economic burden due to frequent monitoring, specialized imaging, and interventions. As life expectancy increases globally, the prevalence of GA secondary to AMD is expected to rise, making it imperative to develop effective treatments to alleviate both individual suffering and socio-economic impact.[8]

This review explores the current and emerging treatments for GA secondary to AMD.

## METHODS

A search to collect relevant manuscripts was performed in PubMed (last search on 9th August 2025), using the following query ("geographic atrophy" [MeSH Terms] OR "atrophic age-related macular degeneration" OR "dry AMD") AND ("treatment" OR "therapy"). The search was limited to articles published from January 2018 onwards and only studies published in English or Portuguese were considered.

Titles and abstracts were initially screened for relevance, followed by a full-text review according to predefined inclusion and exclusion criteria. The inclusion criteria included original research articles evaluating therapeutic interventions for GA secondary to AMD, involving either human subjects or experimental animal models. Studies were required to provide primary data on treatment outcomes. Exclusion criteria included editorials, conference abstracts, and case reports. Studies not primarily focused on therapeutic strategies for GA and studies primarily focused on the neovascular form of AMD were excluded. Articles published in languages other than English and Portuguese were also excluded.

### COMPLEMENT INHIBITORS

Pegcetacoplan is an intravitreal therapy that inhibits C3 and C3b, modulating complement-mediated damage, promoting cell survival and reducing vascular loss. The FILLY was a phase 2 trial conducted in 2020 that evaluated intravitreal pegcetacoplan (15 mg) in 179 patients with GA secondary to AMD and demonstrated consistently slower lesion progression over 12 months in treated eyes ($p<0.05$).[9] These findings supported subsequent phase 3 studies.

Based on these findings, in 2021 and 2022, the phase 3 OAKS and DERBY trials were conducted and evaluated pegcetacoplan 15 mg administered monthly or every other month (EOM) in patients with GA secondary to AMD, respectively. The primary endpoint of both studies was the change in GA lesion growth from baseline to 12 months, assessed by fundus autofluorescence (FAF). Both studies demonstrated a significant slowing of GA progression at 24 months, with combined data showing reductions of 21% (monthly) and 17% (EOM). A post-hoc analysis revealed increased efficacy over time, reaching reductions of 30% and 24% during months 18–24. Despite the structural benefits, no significant improvements in visual acuity were observed. Pegcetacoplan was well tolerated, with low rates of intraocular inflammation and endophthalmitis. However, a higher incidence of new-onset exudative AMD (eAMD) was reported, although this complication was effectively managed with anti-VEGF therapy.[10] These findings led to FDA approval in 2023.

The GALE trial was a 36-month phase 3 extension of OAKS and DERBY that assessed long-term safety and efficacy of pegcetacoplan in 792 patients from prior studies. Patients continued monthly or every-other-month dosing, while those initially assigned to sham crossed over to active treatment. Long-term treatment was generally well tolerated. New-onset eAMD occurred in 4.5% of patients during the first year and remained stable over time, with cumulative rates of 16.0% with monthly dosing and 7.9% with every-other-month dosing at 36 months. Intraocular inflammation incidence was low (3.4% at 36 months), mostly mild and managed with topical steroids, with no reports of vasculitis or retinitis. The incidence of endophthalmitis was low, occurring in 0.03% of patients per injection. Pegcetacoplan demonstrated sustained efficacy over 36 months, with a reduction in geographic atrophy growth of 25% with monthly dosing and 20% with every-other-month dosing compared with sham, corresponding to preservation of 1.49 $mm^2$ and 1.21 $mm^2$ of retinal tissue, respectively. The efficacy of pegcetacoplan was observed across both nonsubfoveal and subfoveal GA lesions, although the magnitude of treatment effect differed according to lesion location. In patients with nonsubfoveal GA, pegcetacoplan reduced GA growth by 32% with monthly dosing and 26% with every-other-month dosing over 36 months, with greater reductions observed during months 24–36 (42% and 28%, respectively). In eyes with subfoveal GA, reductions in GA growth over 36 months were 21% with monthly dosing and 19% with every-other-month dosing, increasing to 31% and 25%, respectively, during months 24–36. The greater treatment effect observed in nonsubfoveal lesions may reflect their faster natural growth rate, allowing a more pronounced measurable reduction in lesion expansion. Patients crossing over from sham experienced a 19% slower GA growth over 12 months, and microperimetry results were consistent with structural outcomes, with fewer new scotomatous points.[11]

Avacincaptad pegol (ACP) is a C5 inhibitor that reduces harmful complement-mediated effects, such as C5a and membrane attack complex formation, while preserving upstream C3 protective activity. GATHER1 was a phase 2/3 trial that randomized 286 participants to intravitreal ACP 1, 2, or 4 mg, or sham. At month 18, GA growth was reduced by 28.1% (ACP 2 mg) and 30% (ACP 4 mg) compared with sham. ACP-treated eyes also showed better preservation of BCVA and LLVA compared with sham. The treatment was generally well tolerated, no endophthalmitis was reported and serious ocular events were very rare. However, conver-

sion to macular neovascularization occurred in 11.9% (ACP 2 mg) and 15.7% (ACP 4 mg), versus 2.7% and 2.4% in the corresponding sham groups.[12]

The GATHER2 phase 3 trial randomized 448 patients to monthly intravitreal ACP 2 mg or sham. At 12 months, ACP significantly reduced GA growth by 14%-18% *versus* sham. Persistent vision loss (≥15 letters) occurred less frequently with ACP (3.1%) compared with sham (7.7%). Ocular adverse events were more common with ACP (49% *vs* 37%) but were generally mild and procedure-related. New onset eAMD developed in 7% of ACP-treated eyes *versus* 4% of sham eyes. The trial is still ongoing, with patients re-randomized after the 12 months to monthly or every-other-month dosing, with year 2 results still pending.[13]

A post-hoc analysis of GATHER1 and GATHER2 showed that at month 12, ACP-treated eyes had lower rates of BCVA loss and a lower risk of persistent vision loss, with consistent benefits across subgroups.[14]

Additional complement-targeted therapies are also under investigation. Vonaprument (ANX007), an intravitreal Fab targeting complement factor C1q and the classical complement pathway, is currently being evaluated in the phase III ARCHER II trial. In the phase II ARCHER study, ANX007 demonstrated protection against vision loss, significantly reducing the risk of persistent ≥15-letter BCVA loss compared with sham.[15] Similarly, cemdisiran, a subcutaneously administered siRNA targeting complement factor C5, is being investigated in the phase III SIENNA trial, either as monotherapy or in combination with pozelimab, to further evaluate complement inhibition in GA secondary to AMD.[16]

## NUTRITIONAL SUPPLEMENTATION

The AREDS and AREDS2 studies evaluated oral micronutrient supplementation in AMD. AREDS enrolled 3640 participants with early or advanced AMD, randomizing them to antioxidants (vitamin C 500 mg, vitamin E 400 IU, β-carotene 15 mg), zinc (80 mg + 2 mg cupric oxide), antioxidants plus zinc, or placebo. AREDS2 included 4203 participants with large drusen or late AMD in one eye, randomizing them to lutein/zeaxanthin (10 mg/2 mg), DHA/EPA (350 mg/650 mg), both, or placebo, and modifications of the original AREDS formula (without β-carotene, reduced zinc, or both). Neither AREDS nor AREDS2 demonstrated a significant effect of supplementation on overall GA area progression, suggesting that micronutrient supplementation does not alter the global rate of GA enlargement. However, secondary analyses showed a potential effect on the pattern of GA expansion, particularly in eyes with noncentral GA. In AREDS, antioxidant supplementation was associated with slower progression toward the central macula compared with no antioxidants (50.7 mm/year *vs* 72.9 mm/year; $p$=0.012). Similarly, in AREDS2 participants not receiving β-carotene, lutein/zeaxanthin supplementation reduced progression toward the central macula compared with no lutein/zeaxanthin supplementation (80.1 mm/year *vs* 114.4 mm/year; $p$=0.011).[17]

Alpha-lipoic acid (ALA) is a nutritional supplement and a potent antioxidant and was evaluated in a phase 2 trial at a dose of 1200 mg orally daily. It was generally well tolerated despite more frequent gastrointestinal events. Despite this, the treatment showed no significant effect on GA lesion growth or visual acuity, with similar rates of ≥15-letter loss compared to placebo.[18]

## PHOTOBIOMODULATION

Photobiomodulation (PBM) uses visible to near-infrared light (500–1,000 nm) to stimulate mitochondrial function, enhance ATP production, and promote cellular proliferation and protection, with cytochrome C oxidase as the primary photoacceptor. The LIGHTSITE III study evaluated multiwavelength PBM with the LumiThera Valeda system in patients with dry AMD, defined by the presence of drusen and/or nonfoveal center-involving GA. Importantly, only 11 eyes had noncenter-involving GA at baseline (PBM, n = 6; sham, n = 5), while eyes with center-involving GA were excluded. 148 eyes received either 9 PBM or sham sessions over 3–5 weeks, repeated every 4 months for 24 months, using yellow, red and near-infrared wavelengths (590, 660 and 850 nm, respectively). At Month 13, PBM-treated eyes gained a mean BCVA of 5.4 letters *versus* 3.0 in sham eyes ($p$=0.0204), with a higher proportion achieving ≥5-, ≥10-, and ≥15-letter gains (PBM-treated *vs* sham, 55% *vs* 40.8, 26.4% *vs* 14.9%, and 5.5% *vs* 1.9% *vs* 40.8%, 14.9%, and 1.9%), and vision loss being more frequent in the sham group. BCVA gains were statistically significant and sustained, and secondary outcomes such as low-luminance BCVA, contrast sensitivity, reading performance, and VFQ-25 scores also remained stable, indicating preserved visual function. PBM-treated eyes showed minimal sub-RPE drusen volume change (0.006 $mm^3$ *vs* 0.049 $mm^3$ in sham) and a lower incidence of new GA (1.1% *vs* 10%). Among the small subgroup of eyes with GA at baseline, GA lesion area increased numerically less with PBM than with sham (1.16 *vs* 1.48 at Month 13), but the difference was not statistically significant (P = 0.75), substantially limiting conclusions regarding the efficacy of PBM in established GA. Progression to neovascular AMD was low and mostly occurred in high-risk eyes. PBM was well tolerated: only four ocular adverse events were considered treatment-related, all mild or moderate, including three cases of dry eye possibly related to the device. No meaningful changes were observed in perimetry or colour vision.[19]

## OCULAR GENE THERAPIES

Ocular gene therapies offer potential for one-time treatment of retinal diseases. JNJ-81201887 (JNJ-1887), an adeno-associated virus vector (AAV) 2-based therapy delivering soluble CD59 via intravitreal injection, was evaluated over 2 years, in a phase 1 trial in 17 GA patients with dry AMD. The treatment was generally well tolerated, with mostly mild and transient ocular inflammation affecting some patients. No dose-limiting adverse events, retinal vasculitis, endophthalmitis, or new-onset CNV were observed. GA lesion growth was similar across groups, however, the high-dose group showed a trend toward slower progression.[20]

RORA is a nuclear receptor involved in regulating

pathways relevant to AMD, including angiogenesis, lipid metabolism, inflammation, and the complement system. AAV5-hRORA gene therapy, targeting the nuclear receptor RORA, was tested in Abca4$^{-/-}$ mice, a model of dry AMD. Subretinal injection increased RORA expression in photoreceptors and RPE reduced lipofuscin accumulation, improved retinal function, restored CD59 expression in photoreceptors and RPE and decreased sub-RPE APP/amyloid-β deposits. Histology showed preserved retinal structure and no adverse effects were reported.[21]

In vitro primary porcine RPE cells exposed to oxidative stress were treated with AAV2/8-VMD2-ophNdi1, a mitochondrial-targeted gene therapy, which improved mitochondrial function and reduced oxidative stress. In vivo Cfh$^{-/-}$ mice received subretinal injections of the therapy and after 8 months, treated eyes showed enhanced photoreceptor function and reduced ROS levels ($p$<0.05), with a trend toward a thicker outer nuclear layer and higher cone count, although differences were not statistically significant. In a $NaIO_3$- induced acute RPE damage model, treated eyes showed improved visual tracking, but ERG and histology indicated only partial functional benefit under severe oxidative stress.[22]

## STEM CELL-BASED THERAPIES

The CPCB-RPE1 subretinal implant consists of an ultrathin parylene membrane supporting a polarized monolayer of RPE cells derived from a human embryonic stem cell line. It was evaluated in 15 GA patients in a phase 1/2a trial, without HLA matching and using only short-term immunosuppression. Immune monitoring after 1 year showed minimal donor-specific antibody formation, with only one patient developing a weak antibody response to a single HLA class II allele. Histology demonstrated long-term survival of the transplanted RPE for over two years, with retention of a mature and polarized phenotype, expression of functional proteins and structural integration with photoreceptors.[23] Safety outcomes were also favourable, with some initial complications (subretinal haemorrhage and edema, retinal detachment, and RPE detachment) being reduced in the subsequent patients through procedural refinements. No choroidal neovascularization or sustained inflammation was reported. While significant visual improvements were unlikely due to advanced disease in the participants, more implanted eyes gained >5 ETDRS letters compared to non-implanted contralateral eyes (27% *vs* 7%, $p$=not significant), and fewer implanted eyes lost >5 letters (33% *vs* 47%, $p$=not significant).[24]

In preclinical studies, hiPSC-RPE cells transplanted into a pig model of GA were later detected in 60% of animals, formed organized RPE-like layers, expressed key functional markers, and interacted with photoreceptors, particularly in healthier retinal regions, further supporting the potential of RPE cell-based therapies for GA.[25]

Palucorcel (CNTO-2476) is a cell-based therapy derived from human umbilical tissue and preclinical studies demonstrated RPE support and retinal preservation. In a Phase 2b study, a single subretinal dose was delivered via a novel suprachoroidal system, which was successfully performed and generally well tolerated. Despite this, no meaningful visual or anatomical benefit was observed, and some patients experienced sustained vision loss. Subretinal delivery via the suprachoroidal space is feasible, however, further development of palucorcel for geographic atrophy has been discontinued.[26]

## ADDITIONAL INVESTIGATIONAL THERAPIES

Several other therapeutic strategies have been explored. Brimonidine, a highly selective α2-adrenergic receptor agonist with neuroprotective properties, modestly reduced GA growth in the phase IIb BEACON trial, particularly in eyes with larger baseline lesions, although it did not prevent visual acuity loss. The study was terminated early due to a lower-than-expected progression rate.[27] Fludrocortisone acetate (FCA), administered intravitreally (1–2 mg) in patients with GA, was well tolerated and showed a trend toward reduced lesion progression, although not statistically significant.[28] Inducing RPE autophagy without mTOR inhibition has emerged as a promising retinal-protective approach. Flubendazole (FLBZ), an FDA-approved antihelminthic, enhanced RPE autophagy, reduced drusen-associated apolipoprotein release, supported photoreceptor metabolism, and decreased lipofuscin accumulation, highlighting its potential role in dry AMD.[29] Elamipretide, a mitochondria-targeted peptide administered by subcutaneous injection, reduces oxidative stress and improves mitochondrial function and is currently being evaluated in the phase III ReNEW trial. In the phase II ReCLAIM-2 study, elamipretide significantly reduced progression of total ellipsoid zone attenuation by 43% and partial ellipsoid zone attenuation by 47% after 48 weeks, suggesting preservation of photoreceptor integrity.[30] Subcutaneous injections of Sefaxersen (10 or 20 mg), a GalNAc-conjugated antisense oligonucleotide that inhibits complement factor B, were evaluated in 54 healthy volunteers in a phase 1 study, where it showed a dose-dependent inhibition of the alternative complement pathway with up to a 69% reduction in factor B levels after repeated dosing. The treatment was well tolerated, with no significant safety concerns, supporting the ongoing phase 2 trial in GA secondary to AMD.[31]

In contrast, several other therapies have been evaluated but failed to demonstrate clinical benefit in GA. Emixustat hydrochloride, an oral RPE65 inhibitor, was evaluated in a phase 2b/3 trial, minocycline, a tetracycline antibiotic with anti-inflammatory and neuroprotective properties, was evaluated in a phase 2 trial and lampalizumab, a complement factor D inhibitor, was evaluated in the phase 3 Chroma and Spectri trials. While they were all generally well tolerated in patients with GA, they showed no effect on disease progression or visual function.[32-34] Galegenimab, an intravitreal anti-HtrA1 Fab, was evaluated in patients with GA in a phase 2 trial, but the study was terminated early due to high rates of intraocular inflammation and on top of the safety concerns, the drug also showed no effect on GA progression or visual function.[35]

## DISCUSSION

In this review, we explored current and emerging therapies for GA secondary to AMD, a condition that until recently had no treatments capable of slowing disease progression.

Complement inhibitors represent the first approved pharmacological intervention capable of altering the course of GA. Pegcetacoplan, a C3 inhibitor, has consistently demonstrated reductions in GA lesion growth, providing structural preservation with benefits lasting up to 36 months. Despite these benefits, improvements in visual function were limited and the risk of exudative AMD was increased, though manageable with anti-VEGF therapy. Similarly, avacincaptad pegol, a C5 inhibitor, has also demonstrated the ability to slow GA progression and modestly protect visual function, with lower rates of persistent vision loss compared with sham. Nevertheless, conversion to neovascular AMD occurred at higher rates in treated eyes. Despite their approval by the FDA, these therapies have not yet been approved by the European Medicines Agency and their overall functional benefits remain modest, somewhat below initial expectations. An important lesson from the pivotal complement inhibitor trials concerns the selection of efficacy outcomes. These studies primarily assessed GA progression based on lesion area measured by FAF. Although FAF is a well-established and reproducible method for quantifying established atrophy, it mainly captures the two-dimensional expansion of RPE loss and may not fully reflect photoreceptor degeneration or visual function. OCT-based assessment of outer retinal integrity, particularly ellipsoid zone and RPE loss, may provide a more sensitive measure of disease progression and treatment response. The discrepancy between the reduction in GA lesion growth and the limited functional benefits observed with complement inhibitors highlights the need for future trials to combine FAF-based lesion area with OCT biomarkers and functional outcomes. These limitations highlight the need for further research to optimize treatment timing, explore potential combination strategies, and ensure long-term safety, particularly regarding neovascular conversion.

Several new therapies are currently under investigation exploring different biological pathways to slow disease progression and protect retinal function. Nutritional supplements, especially antioxidant formulations and lutein/zeaxanthin, have demonstrated small but measurable benefits in slowing GA progression and preserving visual acuity, playing a supportive role in the treatment of GA. Photobiomodulation has emerged as a non-invasive therapeutic approach, showing modest visual improvements, minimal drusen volume change and lower incidence of new GA lesions, potentially making it a safe and convenient treatment option. Mitochondria-targeted therapies, particularly elamipretide, have also emerged as promising approaches. Although ReCLAIM-2 did not demonstrate a reduction in GA enlargement, preservation of the ellipsoid zone suggests that mitochondrial protection may preserve photoreceptor integrity before irreversible retinal atrophy develops. Ocular gene therapies also represent a promising advancement and may offer a one-time treatment for retinal diseases. Early testing of JNJ-81201887, designed to deliver soluble CD59, was generally well tolerated and showed a trend toward slower lesion progression, although functional improvements were limited. Other preclinical studies evaluating ocular gene therapies also showed encouraging findings, but further studies are required to confirm their efficacy and safety in humans. Cell-based therapies are being explored as a regenerative strategy for GA. Early clinical studies using subretinal RPE implants have shown good tolerability, long-term survival of the transplanted cells and signs of structural integration with host photoreceptors, with some patients experiencing modest visual gains. Although still in early stages, these approaches offer a promising foundation for future regenerative strategies to slow degeneration and potentially restore retinal function.

Despite these advances and the emergence of multiple therapeutic strategies, GA remains a profoundly debilitating condition, and current treatments provide only partial benefits. There is still a critical unmet need for therapies that can more effectively slow, stop or even reverse disease progression.

## CONCLUSION

Recent advances in GA management have introduced therapies that, for the first time, can meaningfully influence lesion progression. Approved treatments, such as pegcetacoplan and avacincaptad pegol, offer durable structural benefits, yet functional improvements remain limited, and long-term safety concerns persist, particularly regarding neovascular conversion. It is important to note that in Europe, these drugs are still pending approval. Other approaches are being explored, including nutritional supplements, photobiomodulation, mitochondria-targeted therapies and emerging gene and cell-based therapies. These strategies show potential for preserving and even restoring retinal function and may serve as complementary options to existing treatments, although most remain largely experimental. Overall, GA secondary to AMD remains a debilitating and progressive condition, highlighting the urgent need for more effective therapies. Continued innovation and optimization of treatment strategies are essential to achieve meaningful outcomes and improve the quality of life of affected patients.

## CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

All authors contributed to the conception and design of the study, literature review, drafting and critical revision of the manuscript.

All authors approved the final version of the manuscript for publication and assume responsibility for all aspects of the work, ensuring the accuracy and integrity of the data presented.

Todos os autores contribuíram para a conceção e planeamento do estudo, a revisão da literatura, a redação e a revisão crítica do manuscrito.

Todos os autores aprovaram a versão final do manuscrito para publicação e assumem responsabilidade por todos os aspetos do trabalho, garantindo a exatidão e a integridade dos dados apresentados.

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