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# Therapeutic innovations for geographic atrophy: A promising horizon

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This mini review spotlights the most promising treatments for geographic atrophy, the advanced form of age-related macular degeneration, often resulting in severe and irreversible vision loss. The pathophysiology is complex, and various therapeutic strategies, including anticomplement therapies, gene therapies, cell-based interventions, and artificial intelligence–driven diagnostics are discussed.

Anticomplement therapies (antifactors C3 and C5) showed promise in reducing the inflammatory response and the progression of the atrophy. Gene therapies, targeting specific genetic mutations, are under development to correct underlying defects and potentially reverse disease progression. Cell-based therapies are gaining momentum, with early studies indicating encouraging results in the replacement of damaged retinal pigment epithelium cells.

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**Abbreviations**
AAV, adeno-associated virus; AI, artificial intelligence; AMD, age-related macular degeneration; ARMS2, age-related maculopathy susceptibility 2; anti factors C3 and C5, antifactors Complement 3 and Complement 5; BCVA, best corrected visual acuity; CFI, Complement Factor I; CFH, Complement Factor H; GA, Geographic Atrophy; EMA, European Medicines Agency; EOM, every other month; hESC, human embryonic stem cell; iPSC, induced pluripotent stem cell; MAC, membrane attack complex; OCT, optical coherence tomography; ReST, research and safety in therapeutics; RORA, retinoic acid receptor–related orphan receptor A; ROS, reactive oxygen species; RPE, retinal pigment epithelium.

## Introduction

Geographic atrophy (GA), an advanced form of age-related macular degeneration (AMD), is a severe threat to visual health, often resulting in irreversible vision loss [1,2]. AMD is characterized by the accumulation of drusen in the macular region and progresses to the degeneration of various retinal layers, ultimately leading to subfoveal GA and central vision loss [3].

As the population ages, the incidence of GA is increasing [4]. Fortunately, advances in our understanding of GA's pathogenesis have led to the development of new treatments [5]. Various therapeutic approaches, including complement inhibition, cell-based and gene therapies, and neuroprotection, have been explored. In this review, we will discuss the latest therapeutic innovations and emerging strategies for managing and potentially reversing GA.

### Pathophysiology of geographic atrophy

To fully appreciate the significance of therapeutic innovations, it is essential to understand the underlying mechanisms of GA. GA is an advanced manifestation of AMD, which primarily affects the elderly and presents in early stages with drusen and pigmentary changes [6]. GA is characterized by the progressive degeneration of retinal pigment epithelium (RPE) and photoreceptor cells [2], leading to anatomical and functional changes, including macular atrophy and irreversible central vision loss [2].

Several key pathophysiological factors contribute to GA's development and progression. A fundamental aspect of GA's pathogenesis is RPE dysfunction, which is responsible for maintaining retinal health [7]. Impaired phagocytosis of photoreceptor outer segments results in toxic by-product accumulation, drusen formation, and eventual loss of the photoreceptor and RPE layers [8]. AMD has been associated with immune cells (macrophage) infiltration in the photoreceptor cell layer and around GA lesions [9]. Commonly, in healthy individuals, the central photoreceptor cell layer and the subretinal space are devoid of macrophages [10–12].

Chronic inflammation in GA is initiated by drusen accumulation, involves complement activation, cytokine release, and immune cell infiltration (macrophage), intensifying tissue damage and promoting cell loss [8,13]. For a comprehensive review on the role of infiltrating mononuclear phagocytes and macular degeneration, a review has been published [9].

Dysregulation of the complement system is central to GA's pathophysiology [2]. Genetic variations in complement factors, such as complement factor H (CFH), complement factor I (CFI), complement component 3 (C3), and C5 predispose individuals to impaired regulation, contributing to chronic inflammation and RPE damage [14,15].

Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and cellular antioxidant defense mechanisms, plays a crucial role [16]. Mitochondrial dysfunction is a significant source of ROS in AMD [17]. Increased oxidative stress contributes to retinal cell damage. Moreover, oxidative stress is also a consequence of aging and environmental factors, further damaging RPE and photoreceptor cells [16].

Genetic factors also significantly influence the development and progression of AMD, including GA [14,18]. Variants in genes such as CFH, age-related maculopathy susceptibility 2 (ARMS2), CFI, and C3 have been strongly associated with increased susceptibility to AMD and GA [19].

Understanding these complex pathological mechanisms is crucial for developing targeted therapeutic strategies to slow or halt GA progression. As the disease advances, strategies focusing on modulating complement dysregulation, mitigating oxidative stress, and preserving retinal cell viability hold promise for potential treatments to alleviate the burden of GA on affected individuals. In the pursuit of effective interventions for GA, researchers are exploring a spectrum of promising therapeutic approaches that are currently being evaluated in clinical trials.

## Promising therapeutic approaches

Currently, several therapeutic strategies are under investigation with the goal of preventing, slowing down, or halting the progression of GA and potentially restoring vision. In the following, we will provide an overview of the most promising therapeutic approaches. Table 1 summarizes the principal clinical trials evaluating treatments for GA. Some studies have been discontinued or terminated because the primary endpoints were not met. In this minireview, we will only present ongoing studies or with positive results aiming to outline the most promising approaches for GA treatment.

### Anticomplement therapies

The first drugs ever approved for GA treatment are anticomplement therapies [20–22]. The complement system's dysregulation is a central driver of inflammation and cell death in GA. Recent clinical trials have demonstrated the effectiveness of complement inhibitors, such as pegcetacoplan and avacincaptad pegol, administered by intravitreal injections (for an extensive review on complement system therapies for AMD, see Ref. [23]). These treatments slow down the progression of GA by reducing the inflammatory response. Their mechanism is related to prevent the formation of the membrane attack complex (MAC), a key contributor to complement-induced cell damage [24]. These therapies represent newfound hope for slowing the natural course of the disease.

#### *Complement factor C3 inhibition*

Pegcetacoplan (APL-2, Syfovre® from Apellis Pharmaceuticals, USA) is a pegylated pentadecapeptide acting as selective inhibitor of C3 on all three complement pathways (classical, alternative, and lectin pathways) [25]. The FILLY phase-2 trial demonstrated that monthly intravitreal APL-2 injections could reduce GA growth compared to a sham group by 29% [26]. Despithe that, pegcetacoplan increased the frequence of exsudative AMD in around 20% of the study eyes compared to sham (20.9% in the monthly group and 8.9% in the every-other-month [EOM] group, respectively) [26], a condition that led to discontinuation of study treatment in those patients. The OAKS and DERBY phase-3 studies, involving 1258 GA patients, further evaluated the safety and efficacy of pegcetacoplan [27]. Results from both trials revealed a statistically significant reduction in lesion growth rate compared to the sham group at 24 months [28]. In particular, the OAKS study showed that, by month 24, pegcetacoplan administration reduced GA lesion growth compared to sham by 22% and 18% in monthly and EOM treatment groups, respectively. In the DERBY trial, these percentages were slightly lower, at 19% and 16% for the monthly and EOM groups, respectively [27,29,30]. There was no benefit on visual function for both groups. During the trials, 3.8% and 2.1% of participants developed intraocular inflammation in the monthly and EOM group, respectively, with no reported cases of retinal vasculitis or occlusive retinal vasculopathy, and 10% and 7% of patients experienced vitreous floaters in the monthly and EOM arms, respectively. Ischemic optic neuropathy was reported in 1.7% and 0.2% of participants treated monthly and EOM groups, respectively [30]. New-onset choroidal neovascularization was reported in 11%, 8%, and 2% of patients in OAKS, and in 13%, 6%, and 4% of patients in DERBY, receiving pegcetacoplan monthly, pegcetacoplan EOM, and sham, respectively, at 24 months [30]. Recently, the American Society of Retina Specialists (ASRS) Research and Safety in Therapeutics (ReST) Committee and an

**Table 1**

**Overview of complement and gene- and cell-based therapies. Clinical studies completed, ongoing, or terminated.**

| TRIAL | Compound/molecule | Sponsor | Mechanism | Trial ID | Phase and status | Comments | Referencess |
|---|---|---|---|---|---|---|---|
| FILLY | Pegcetacoplan (APL-2, Syfovre®) | Apellis Pharmaceuticals, USA | Pegylated pentadecapeptide, selective inhibitor of C3 | NCT02503332 | Phase II—completed | FDA approved in February 2023 | [26] |
| OAKS | Pegcetacoplan (APL-2, Syfovre®) | Apellis Pharmaceuticals, USA | Pegylated pentadecapeptide, selective inhibitor of C3 | NCT03525613 | Phase III—completed | FDA approved in February 2023 | [27–29,69] |
| DERBY | Pegcetacoplan (APL-2, Syfovre®) | Apellis Pharmaceuticals, USA | Pegylated pentadecapeptide, selective inhibitor of C3 | NCT03525600 | Phase III—completed | FDA approved in 2023 (Ref 20) | [27–29,69] |
| GATHER1 | avacincaptad pegol (Izervay®, Zimura®) | Iveric Bio, USA | Pegylated RNA aptamer, inhibits C5 cleavage | NCT02686658 | Phase II/ III—completed | FDA approved in August 2023 | [35,37] |
| GATHER 2 | avacincaptad pegol (Izervay®, Zimura®) | Iveric Bio, USA | Pegylated RNA aptamer, inhibits C5 cleavage | NCT04435366 | Phase III—completed | FDA approved in August 2023 | [35,37] |
| Danicopan | Danicopan (ALXN2040) | Alexion Pharmaceuticals Inc., USA | Inhibition of complement factor D | NCT05019521 | Phase II—active | Study completion was estimated for mid-2023 | ClinicalTrials.gov |
| CATALINA | NGM621 | NGM Biopharmaceuticals | Humanized immunoglobulin G1 (IgG1) monocolonal antibody, binds to C3 and inhibits complement activation | NCTO4465955 | Phase II—completed | Primary endpoint not met | [70] |
| CHROMA | Lampalizumab | Hoffmann-La Roche | Antigen-binding fragment that inhibits complement factor D | NCT02247479 | Phase III—terminated | Unlikely to meet primary endpoint | [71–73] |
| SPECTRI | Lampalizumab | Hoffmann-La Roche | Antigen-binding fragment that inhibits complement factor D | NCT02247531 | Phase III—terminated | Unlikely to meet primary endpoint | [71–73] |
| OMASPECT | Lampalizumab | Hoffmann-La Roche | Antigen-binding fragment that inhibits complement factor D | NCT02745119 | Phase III—terminated | Unlikely to meet primary endpoint | ClinicalTrials.gov |
| ARCHER | ANX007 | Annexon Biosciences, USA | C1q inhibitor | NCT04656561 | Phase II—active | Great neuroprotective efficacy, but primary endpoint not met | [74] |
| GOLDEN | IONIS-FB-LRx | Akcea Therapeutics, USA | Complement Factor B inhibitor | NCT03815825 | Phase II—active | results are expected by end of 2024 | [75] |
| AAVCAGsCD59 | AAVCAGsCD59 (JNJ-1887) | Janssen R&D | | NCT03144999 | Phase I—completed | Safety primary endpoint met. | jnj.com & ClinicalTrials.gov |

(*continued on next page*)

**Table 1. (*continued*)**

| TRIAL | Compound/molecule | Sponsor | Mechanism | Trial ID | Phase and status | Comments | Referencess |
|---|---|---|---|---|---|---|---|
| | | | Gene therapy. Stimulation of CD59 production | | | | |
| PARASOL | AAVCAGsCD59 (JNJ-1887) | Janssen R&D | Gene therapy. Stimulation of CD59 production | NCT05811351 | Phase IIb—currently enrolling | results expected by the end of 2025 | ClinicalTrials.gov |
| STARLIGHT | vMCO-010 (virally-carried Multi-Characteristic Opsin) | Nanoscope Therapeutics Inc., USA | Gene therapy, re-expression of the MCO gene | NCT05417126 | Phase II—completed | Study completed end of 2023. Results expected soon- | [50]ClinicalTrials.gov |
| ArMaDa | OCU410 (AAV5-hRORA) | Ocugen Inc., USA | Gene therapy, RORA gene reexpression | NCT06018558 | Phase I/II—recruiting | Completion date estimated for September 2025 | ClinicalTrials.gov and ocugen.com |
| EXPLORE | GT005 | Gyroscope Therapeutics, Novartis | Gene therapy. Downregulation of C3b by overexpressing the complement factor I gene | NCT04437368 | Phase II—terminated | Terminated because of futility—very unlikely to meet efficacy outcome | ClinicalTrials.gov |
| HORIZON | GT005 | Gyroscope Therapeutics, Novartis | Gene therapy. Downregulation of C3b by overexpressing the complement factor I gene | NCT04566445 | Phase II—terminated | terminated because of futility—very unlikely to meet efficacy outcome | ClinicalTrials.gov |
| ASP7317 | ASP7317 and tacrolimus | Astellas Pharma Inc. | Transplantation of hESC-derived RPE cells and immunosuppressive drug to avoid rejection | NCT03178149 | Phase I—recruiting | study completion estimated for end 2024 | ClinicalTrials.gov |
| California Project to Cure Blindness | CPCB-RPE1 | Regenerative Patch Technologies | of hESC-RPE cells grown on a synthetic parylene substrate, mimicking Bruch's membrane | NCT02590692 | Phase I/II | Phase 2b trial will be launched soon | [35,36] ClinicalTrials.gov, cirm.ca.gov |
| OpRegen | OpRegen | Lineage cell Therapeutics, Hoffman-LaRoche | RPE cells derived from hESC | NCT02286089 NCT05626114 | Phase I/II—ongoing Phase IIa—recruiting | Phase 2a study completion date by mid-2029 | ClinicalTrials.gov |
| RPESC-RPE-4W | RPESC-RPE-4W | Luxa Biotechnology | allogeneic RPESC-derived RPE cells | NCT04627428 | Phase I/IIa—recruiting | Study completion expected in May 2025 | ClinicalTrials.gov |

Blue = complement therapies; light blue = complement therapies not cited in the main review text; orange = gene therapies; dark orange = gene therapies not cited in the main review text; green = cell-based therapies. AAV = adeno-assocaited virus; FDA = Food and Drug Administration; hESC = human endotelial-derived stem cell; MCO = multicharacteristic opsin; RORA = retinoic acid receptor–related orphan receptor A; USA = United States of America; CPCB-RPE1 = California Project to Cure Blindness—Retinal Pigment Epithelium 1; RPESC = retinal pigment epithelium stem cell.

independent expert panel reported the results of a postmarketing survey on 14 eyes of 13 patients with retinal vasculitis occurring after intravitreal pegcetacoplan injection [31].

Following the completion of the phase-3 OAKS and DERBY trials, the Food and Drug Administration (FDA) approved pegcetacoplan (15 mg; 0.1 ml of 150 mg/ml; Syfovre®) for the treatment of GA associated with AMD in early 2023 [30,32,33], based on anatomic endpoints. On the other side, recently European Medicines Agency (EMA) expressed negative opinion of the same drug because the clinical trials failed to show any functional improvement after two years [31,34].

### *Complement factor C5 inhibition*

Various studies focus on targeting the C5 component of the complement pathway. A phase-2 randomized controlled trial (GATHER1) investigated the effects of intravitreal injections of avacincaptad pegol (Izervay®, also called Zimura®, Iveric Bio, an Astellas Company, Parsippany, NJ, USA) [35]. This compound, a pegylated RNA aptamer, inhibits C5 cleavage and blocks the formation of terminal fragments, ultimately reducing inflammasome activation and MAC formation [35]. The GATHER1 study (a phase-2 trial) met the specified primary endpoint of reducing the growth rate of GA over 12 months, with a 27% reduction in the 2-mg group and a 28% reduction in the 4-mg group [36]. The 18-month safety analysis found no adverse events or cases of inflammation [36]. The trial proceeded to phase 3 with the GATHER 2 study (ClinicalTrials.gov identifier: NCT04435366), involving 448 nonsubfoveal GA patients who received either sham or 2 mg monthly avacincaptad pegol [37]. The results indicate that monthly injections of avacincaptad pegol 2 mg were well-tolerated, and in 14% of treated eyes, GA growth rate slowed over 12 months compared to sham treatment [37]. Also, in this case, the clinical trials failed to show any functional benefit after one year of treatment. Seven percent of treated patients compared to 4% of sham developed macular neovascularization at the end of year one [37]. Avacincaptad pegol (2 mg; 0.1 ml of 20 mg/ml; Izervay®) was recently approved by the FDA in August 2023 for the treatment of GA secondary to AMD, ([21]) only based on anatomic endpoints.

### *Other complement therapies*

Danicopan (ALXN2040, Alexion Pharmaceuticals), is an investigational drug in development, primarily designed as an add-on to two C5 inhibitor therapies for patients with paroxysmal nocturnal hemoglobinuria (Ultomiris and Soliris) [38] that is now under investigation as monotherapy for GA in a phase-2 clinical trial (NCT05019521). This drug belongs to the first-in-class inhibitor of complement factor D, an essential enzyme for the activation of the alternative pathway [39,40]. A recent preclinical study, demonstrated that the orally administered drug in preclinical animal models is capable of crossing the blood–retina barrier, distributing in the neural retina, and binding to melanin [39]. This drug holds a great potential from several aspects. Danicopan could represent a better therapeutic strategy for GA patients who would not need intravitreal injections, thereby, potentially decreasing the risks related to intravitreal injections and potentially increasing patient's compliance. Moreover, this strategy allows for simultaneous treatment of both eyes, which could be beneficial, considering that in GA, bilateral eye involvement is common [39]. The phase-2 clinical trial is expected to be completed by August 2025.

## Gene therapies

Genetic factors play a significant role in AMD and GA [14,18,19]. AMD has a strong genetic component, with the complement factor being the most implicated [41]. Two main genetic loci associated with AMD and GA formation are 1q31 and 10q26 gene polymorphisms, corresponding to the complement pathway and HtrA1/ARMS2 (serine peptidase 1/age-related maculopathy susceptibility 2) [42,43]. Gene therapies targeting specific genetic mutations associated with GA are in development. These therapies aim to correct underlying genetic defects and potentially slow or even reverse disease progression.

Adeno-associated virus (AAV)CAGsCD59 (JNJ-1887, Janssen research and development) is a gene therapy delivered via intravitreal injection [44]. CD59 inhibits the formation of MAC, and patients with AMD generally have lower levels of CD59 [45]. This innovative therapy stimulates cells to produce CD59, inhibiting MAC formation and preventing cell damage. The drug was recently evaluated in a phase-I clinical trial, where patients received three escalating doses of JNJ-1887 ($3.56 \times 10^{10}$ vg/eye; $1.07 \times 10^{11}$ vg/eye; $3.56 \times 10^{11}$ vg/eye) via a single intravitreal injection [44]. The study met the primary safety endpoint for all JNJ-1887 doses (N = 17), and efficacy measures supported the compound's effectiveness in reducing GA lesion growth rates, demonstrating a continuous decline in lesion growth over six-month increments. A phase-2b clinical trial (PARASOL, ClinicalTrial.gov identifier: NCT05811351) is currently enrolling approximately 300 participants with the aim of evaluating the change in GA lesion growth in eyes treated with JNJ-1887 compared to a sham control. This therapy holds promise, with results expected by the end of 2026.

GT005 (Gyroscope Therapeutics, Novartis) is an investigational gene therapy designed to downregulate C3b by overexpressing the CFI gene [46]. EXPLORE (NCT04437368) and HORIZON (NCT04566445) are two phase-2 clinical trials that evaluated the effect of a single subretinal injection of GT005 in people with GA

secondary to dry AMD (75 and 180 participants respectively). Despite GT005 was reported to be safe and well tolerated in mice and nonhuman primates [46], these studies were terminated in September 2023 because of achievement of futility criteria (from Novartis news of 11 Sept 2023).

Single-intravitreal injection of virally carried multicharacteristic opsin (vMCO-010 optogenetic therapy, Nanoscope Therapeutics) is currently being investigated in the STARLIGHT phase-2 clinical trial (NCT05417126). This study will evaluate the single dose level of vMCO-010 in 6 subjects with Stargardt's disease. Stargardt disease is an autosomal recessive retinal dystrophy caused by a mutation of ABCA4 (adenosine triphosphate-binding cassette, subfamily A, member 4) gene that encodes an integral transmembrane protein expressed in retinal photoreceptors [47]. Dysfunction of this gene ultimately results in macular degeneration [48,49], a common feature of GA [2]. Since Stargardt disease appears clinically similar to GA [48], GA patients could potentially benefit from this innovative genetic therapy that, thanks to the re-expression of the MCO-010 opsin, restores light sensitivity in retinal bipolar cells [47]. The trial was recently completed, and results are awaited soon [50].

OCU410 (AAV5-h retinoic acid receptor—related orphan receptor A [RORA], Ocugen$_{TM}$) is another recent genetic therapy that is currently being investigated in a phase-I/-II clinical trial (ArMaDa trial, NCT06018558). OCU410 is a modified gene therapy developed for dry AMD that will target multiple pathways, thanks to the re-expression of the RORA gene. The RORA protein plays an important role in lipid metabolism and oxidative stress and was demonstrated to have a potential role in AMD pathophysiology [51]. The safety and efficacy of a single-intravitreal injection of OCU410 will be evaluated in the multicentre phase-I/-II study (From Ocugen, Inc. news as of December 13th 2023).

## Cell-based therapies

Cell-based therapies are categorized into stem-cell-based and non-stem-cell-based approaches. Stem-cell-based therapies aim to replace degenerated RPE cells, whereas non-stem-cell-based therapies introduce cells that release factors supporting photoreceptor survival and function [52].

Stem-cell therapy and RPE transplantation are emerging as potential treatments for GA [28,53]. These approaches target the replacement of damaged RPE cells to restore visual function, with early studies showing promise [54,55]. However, long-term safety and efficacy are still under investigation [55,56].

### *Stem cell therapies*

One promising approach involves induced pluripotent stem cells, which can be differentiated into RPE cells and transplanted into the retina [57]. While early studies suggest potential for vision improvement, challenges such as immune rejection and tumorigenesis must be addressed [58].

### *Human embryonic stem cell–derived RPE transplantation*

A phase-1 clinical study is underway (ClinicalTrials.gov ID: NCT03178149), involving the transplantation of human embryonic stem cell (hESC)-derived RPE cells (ASP7317, Astellas Pharma) into the macula of patients with dry AMD. An immunosuppressive drug (tacrolimus) is administered to prevent cell rejection. The study assesses the safety and efficacy of three dose levels in two groups of patients with varying degrees of vision loss, with a study completion date estimated for the end of 2024 (Clinicaltrials.gov).

### *California Project to Cure Blindness—Retinal Pigment Epithelium 1*

In a phase-I/-II study (ClinicalTrial.gov ID: NCT02590692), researchers are investigating a composite subretinal implant known as California Project to Cure Blindness—Retinal Pigment Epithelium 1. This implant comprises a polarized monolayer of hESC-RPE cells grown on a synthetic parylene substrate, mimicking Bruch's membrane [59], which typically degenerates during AMD [60]. Five patients were enrolled in the phase-I clinical trial, and four of them successfully received the implant [59]. Preliminary findings on safety and tolerability are promising; none of the implanted eyes presented vision loss, one eye has reported therapeutic effects on visual acuity (improvement of 17 letters), and two eyes showed improved fixation [59,61]. These first preliminary results indicate efficacy of this subretinal implant. However, larger studies are currently being performed to confirm the efficacy and safety of the implant for treating GA.

### *OpRegen therapy*

A phase-I/-II trial is ongoing, using OpRegen, a cell-based product composed of RPE cells derived from hESC (Lineage Cell Therapeutics and Hoffman-LaRoche; NCT02286089). OpRegen is administered via intraocular injection into the subretinal space. The trial assesses safety, tolerability, and initial efficacy, with preliminary data showing evidence of improved outer retina structure and visual function in GA patients even after 4 years of follow-up (Clinicaltrials.gov). These results suggest OpRegen may support the remaining retinal cells in the atrophic area by counteracting RPE cell loss and dysfunction. The study also identifies optical coherence tomography (OCT) imaging with segmentation analysis as more advantageous than FAF for

assessing retinal integrity after OpRegen treatment (from lineagecell.com/products-pipeline/opregen).

The preliminary findings from the phase-I/-II trial will be confirmed in a phase-IIa clinical study (Clinicaltrials.gov, NCT05626114) for the same intervention with OpRegen, currently recruiting patients with an estimated study completion date in mid-2029.

#### *RPESC-RPE-4W cells*

A recent Phase I/IIa trial (Clinicaltrials.gov, NCT04627428) is assessing the safety, tolerability, feasibility, and preliminary efficacy of RPESC-RPE-4W cells (Luxa Biotechnology), consisting of allogeneic RPE stem cell (RPESC)-derived RPE cells [62]. These cells were isolated from the RPE layer of human cadaveric eyes. The trial is also evaluating the feasibility and preliminary efficacy of subretinal RPESC-RPE-4W on dry AMD using a dose-escalation approach (from Clinicaltrials.gov). Study completion is expected in May 2025 (Clinicaltrials.gov).

### Artificial intelligence and imaging

Artificial intelligence (AI)-driven diagnostic tools and advanced imaging techniques could transform the early detection and monitoring of GA, leading to timely interventions and improved patient outcomes [63]. These tools are invaluable for identifying high-risk patients and tracking disease progression. Machine-learning algorithms can analyze retinal images, such as OCT scans, to detect, classify, and quantify GA [64,65]. They will also play a key role in evaluation of efficacy of new drugs, setting new outcome parameters for future clinical trials.

AI-driven image analysis offers precise tracking of GA progression, aiding in the identification of high-risk patients and the assessment of treatment responses in clinical trials [66]. These technologies allow AI algorithms to analyze various types of multimodal imaging, helping to correlate structure with function, which is becoming increasingly important for GA management [64,67]. For example, in a recent study (the phase 2 FILLY trial), researchers used deep-learning-based algorithms to automatically quantify photoreceptor loss based on OCT images [64]. This approach proved to be reliable for monitoring disease activity. Additionally, a fully automated analysis of retinal OCT is able to perform segmentation of GA atrophy and its subtypes at a level similar to manual assessment. This method, proposed by Zhang et al. [64], holds promise for clinical practice for the detection and quantification of GA, as well as evaluation of efficacy of new drugs.

## Challenges and future directions

While promising therapeutic innovations are on the horizon, several challenges must be addressed to translate them into effective treatments for GA. These include safety concerns, patient selection, and multifactorial pathogenesis of the disease. In fact, ensuring the long-term safety of therapies, particularly in the context of gene editing and cell transplantation, remains a critical consideration. Moreover, identifying the most suitable candidates for specific therapies based on genetic, clinical, and imaging data is crucial for optimizing treatment outcomes. Finally, given the multifaceted nature of GA, combination therapies targeting multiple pathways may be necessary for optimal results.

## Conclusion

GA represents a significant challenge in ophthalmology, with the potential to cause severe and irreversible vision loss. However, the landscape of GA therapeutics is rapidly evolving, offering newfound hope for patients. Recently, two new drugs have become available for GA treatment (Syfovre® and Izervay®) in the US, while promising developments in anticomplement therapies, cell-based interventions, gene therapies, and AI-driven diagnostics are currently under investigation (see Table 1). These approaches hold the potential to reshape the future of GA management in the long term. Nevertheless, further studies are warranted to achieve positive effect in terms of not only slowing down the growth rate of GA lesions but also maintaining or improving visual acuity. However, best corrected visual acuity does not reflect disease progression in GA; therefore, other functional endpoints needs to be studied to evaluate efficacy of new treatments for GA [66,68]. At the same time, a careful surveillance of side-effects is mandatory. The assessment of safety and effectiveness of new treatments is an important step that still needs to be comprehensively investigated. Collaborations between researchers, clinicians, and the pharmaceutical industry are essential for advancing these innovations and addressing the complex challenges associated with GA. As research continues to unfold, the dream of effective GA therapies transitioning from the realm of possibility to reality has already begun.

## Author contributions

**Eva C. de Oliveira Figueiredo:** writing—original draft preparation; writing review and editing.
**Chiara Eandi:** conceptualization, writing—review and editing.
**Claudio Bucolo:** writing—review and editing.

## Declaration of competing interest

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