

The Use of Neuroprotective Agents in Treating Geographic Atrophy

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Abstract

Geographic atrophy (GA) secondary to age-related macular degeneration accounts for close to one-quarter of cases of legal blindness in the USA and the UK. Despite this notable disease burden, the pathophysiology of GA is complex and not fully understood, and there is currently no approved treatment to prevent or slow its progression. GA is heterogeneous in its appearance and extent, and underlying associated traits such as drusen and complement factor polymorphisms vary between patients and by ethnicity, posing a challenge for treatment development. The root cause of vision loss in GA is photoreceptor death; therefore, protecting photoreceptors from damage and delaying their degeneration are key to successful GA treatment. There are multiple neuroprotective pathways that may contribute to protecting photoreceptors from damage, and compounds that target these pathways include antioxidants, neurotrophic factors, and catalases. However, the efficacy of previously trialled neuroprotective therapies in GA, such as brimonidine, tandospirone, and NT-501, has been inconsistent; this may

be due to their target of action, method of delivery, and/or suboptimal duration of action. Neurotrophic factors, or molecules involved in neuroprotective signalling cascades, may be ideal agents for further investigation for the treatment of GA. Future neuroprotective strategies in GA must focus on the development of agents with a long duration of action that can combat the progression of chronic damage in GA to provide clinically meaningful benefits for patients.

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Introduction

Epidemiology of Geographic Atrophy

Age-related macular degeneration (AMD) is a leading cause of blindness in people aged 50 years and over in the developed world [1–4]. The incidence of AMD and its advanced stages increases exponentially with age [4]; as the global population ages, it is estimated that the prevalence of advanced AMD will rise from 11.26 million cases in 2020 to 18.57 million by 2040 [4, 5].

Advanced AMD can be divided into 2 forms: “wet” AMD (wAMD) and geographic atrophy (GA). wAMD is characterized by the formation of new blood vessels from the choroid into the subretinal or retinal pigment epithe-

lium (RPE) spaces and comprises 3 primary types [6–8]. GA is characterized by progressive atrophy and thinning of the RPE and choriocapillaris, leading to photoreceptor death and vision loss [5, 9–11]. At present, GA affects approximately 5 million people globally, accounting for roughly 25% of cases of legal blindness in the USA and the UK [5, 12]. A meta-analysis published in 2020 indicated that GA is less common in Asian populations compared with European populations, although information on the epidemiology of GA in Asia is limited [13].

Pathophysiology of GA

Although heterogeneous in its appearance and extent, GA often begins as a single parafoveal lesion [14, 15]. GA may form in areas previously occupied by drusen or RPE detachments [14, 16–18]; drusen are extracellular deposits that are located between the RPE and Bruch's membrane [10]. The presence of multiple large drusen increases the probability of developing GA [5], and GA that forms in areas previously occupied by drusen is associated with substantially worse visual outcomes [14]. GA is also associated with morphological changes such as reticular pseudodrusen [16, 18], which are small yellow-white lesions typically located above the RPE [18]. Reticular pseudodrusen have been associated with reduced choriocapillaris flow and density [18] and are more common in eyes with GA or type 3 wAMD (retinal angiomatous proliferation) than those with other advanced forms of AMD (83% and 50% of eyes respectively, vs. 9%) [19]. Eyes with reticular pseudodrusen are more likely to progress to an advanced form of AMD than those with drusen alone [20–22]. The presence of drusenoid pigment epithelial detachments may also precipitate GA, with one analysis showing that drusenoid pigment epithelial detachments have a 50% chance of developing into GA after 7 years [23].

Complement factor polymorphisms are associated with, and are systemically activated in, AMD [24–28]. The complement system is a crucial part of the body's immune system, leading to proteolytic cascades and the release of proinflammatory molecules that target pathogens, resulting in inflammation [28, 29]. Chronic inflammation has been associated with the pathogenesis of GA [30]. Furthermore, complement activation may play a functional role in systemic cardiovascular disease, leading to poor choroidal and ocular perfusion, which could precipitate GA [31, 32]. Although complement is not associated with all cases of GA, one phenotypic subgroup of GA (with large soft drusen and foveal atrophy) is characterized by a high genetic risk score for complement poly-

morphisms [33], and complement proteins have been found in the retina adjacent to some GA lesions [10]. Components of the complement system have been found in drusen, but to date, their relationship with pseudodrusen is less clear [34]. It is also not currently known whether complement proteins lead to the formation of drusen or accumulate as a result of drusen [28]. The presence and phenotype of drusen and pseudodrusen vary by race; for example, Caucasians are more likely to develop large drusen than people of other races [35, 36]. Similarly, the complement polymorphisms that are commonly found in Caucasians have a much lower frequency in Asian populations [37–40]. Ethnic variation in the AMD-associated Y402H complement polymorphism does not correlate with the overall prevalence of AMD, suggesting that different polymorphisms or genes may be risk factors in some populations [40]. Two phenotypic subgroups of GA with low genetic risk scores for complement polymorphisms have been identified: one with foveal atrophy and few drusen, and another with extrafoveal atrophy, reticular pseudodrusen, and a high *ARMS2* genetic risk score [33]. This suggests that the complement system and drusen phenotype are not major drivers of AMD in all populations.

Trials of complement inhibition in patients with GA have shown inconsistent success in slowing GA progression; only pegcetacoplan and avacincaptad pegol have demonstrated a significant reduction in square root GA lesion growth versus sham treatment (0.39 vs. 0.49 mm, $p = 0.044$; 0.32 vs. 0.44 mm, $p = 0.0051$, respectively), but neither were accompanied by a corresponding functional difference in best corrected visual acuity (BCVA) or low-luminance BCVA [41–45]. The limited success of complement inhibitors may partly relate to the ethnic variation in complement polymorphisms.

Disease Burden of GA

GA is associated with considerable disease progression and burden, with patients experiencing a loss of both visual acuity and independence when performing daily tasks. Close to half of all patients with GA are legally blind, with 42% reported as having 20/200 vision or worse [46]. Larger areas of GA are associated with a decreased visual acuity and function, hindering patients' ability to carry out daily tasks [47–50]. Reading speed declines as a function of GA lesion size, location, and growth [50, 51], and GA negatively affects patients' ability to recognize faces [52, 53]. GA also severely impacts patients' ability to drive, limiting their freedom to travel [54]; 66.7% of patients become ineligible to drive within a median time of

1.6 years from their diagnosis [12]. AMD and GA also affect other aspects of patients' quality of life, increasing the risk of depression as well as susceptibility to falls and injuries due to poor visual acuity [55, 56]. As a GA lesion increases in size, skills critical for maintaining quality of life deteriorate, such as reading speed and recognizing faces [50, 51, 57]. Many patients with GA also experience fear related to their condition and the deterioration of their eyesight [48, 49].

Unmet Medical Need

Although acute vision loss due to wAMD responds to treatment and is reversible to some extent, the progressive vision loss that results from GA is irreversible in a substantial proportion of treated patients [8, 9]. As such, the primary goal of GA treatment is to prevent or delay disease progression [58]. Some large trials such as the Age-Related Eye Disease Studies (AREDS/AREDS2) focused on the prevention of advanced AMD [59–61] but included only a small number of patients with GA, yielding little benefit for this population. For example, AREDS included 118 patients with GA, compared with 658 with wAMD and 1,568 with large or extensive drusen [60].

At present, there is no approved pharmacological treatment for preventing the onset or slowing the progression of GA. The slow progress of treatment development may in part be attributed to the lack of adequate in vivo models of GA [62]. In addition, most clinical trials that focused specifically on patients with GA have targeted the complement system. However, the presence of reticular drusen and complement activation vary by population, meaning that anti-complement therapy may not be efficacious in all patients with GA [63–65]. This has prompted investigation into alternative approaches, including anti-inflammatory agents, synthetic vitamin A replacement therapy, visual cycle modulation, and neuroprotection [66–71]. To examine the potential role of neuroprotective treatments in GA, we investigated peer-reviewed journal articles using PubMed and conducted a series of clinical trial database searches using clinicaltrials.gov for studies of GA treatments.

Neuroprotection in GA

Background of Neuroprotection

Neuroprotection entails the preservation, recovery, or regeneration of neuronal function and structure after catastrophic acute injury (e.g., stroke) or chronic ongoing damage (e.g., neurodegeneration) [72, 73]. Although the

symptoms of disease resulting from neural damage vary, many aspects of their pathogenesis are shared, such as inflammation and oxidative stress [74–77]. Investigation into the pharmacological protection of neurons from damage began in the 1980s and focused on stroke and excitotoxic injury [78].

Multiple complex pathways for neuroprotection exist, including the inhibition of neurodegenerative apoptosis, necroptosis, and ferroptosis [79–81]. As such, there are many potential therapeutic approaches for neuroprotection (shown in Fig. 1). These include apelin-13 peptide, which has been shown to protect against further acute damage in a rat model of ischemic stroke through the AMPK/GSK-3 β pathway via AR/G α /PLC/IP3/CaMKK signalling [82], and *N*-acetyl-serotonin treatment, which protects ischemic neural cells in a state of oxygen-glucose deprivation from chronic damage by inhibiting mitochondrial cell death in mice [83]. In addition, the PI3K/Akt pathway is critical in the protection of neural cells against staurosporine-induced apoptosis through the up-regulation of tropomyosin-related kinase (Trk) via nerve growth factor and brain-derived neurotrophic factor (BDNF) in vitro [84]. It is clear that there are many potential mechanisms through which neuroprotection can be achieved.

Antioxidants

Antioxidants may delay or prevent apoptosis, thus preserving neurons [76, 85]. Manganese superoxide dismutase is thought to be a major mechanism by which cells counteract reactive oxygen species (ROS) injury after ischemia [86]. A synthesized mimic of manganese superoxide dismutase significantly increased the in vitro viability of neurons and improved neurological function in an ischemic stroke mouse model ($p < 0.01$ compared with an untreated control group) [86]. Resveratrol and glutathione have also been investigated for their potential neuroprotective effects in retinal ganglion cells [76, 87, 88]. To date, in humans, antioxidants have not been shown to have a significant effect on GA lesion growth; the placebo group in AREDS had a mean lesion growth of 7.89 mm, whereas patients who received antioxidants alone had a mean lesion growth of 6.64 mm ($p = 0.19$) [89]. Furthermore, a trial of OT-551 (a synthesized molecule with antioxidant properties administered via eye drop) failed to show any significant difference in area of GA or drusen between the study and fellow eye ($p > 0.05$) [90]. However, the use of antioxidants, whether through diet or other modern therapeutic methods, could stimulate endogenous protective mechanisms in patients with GA [85].

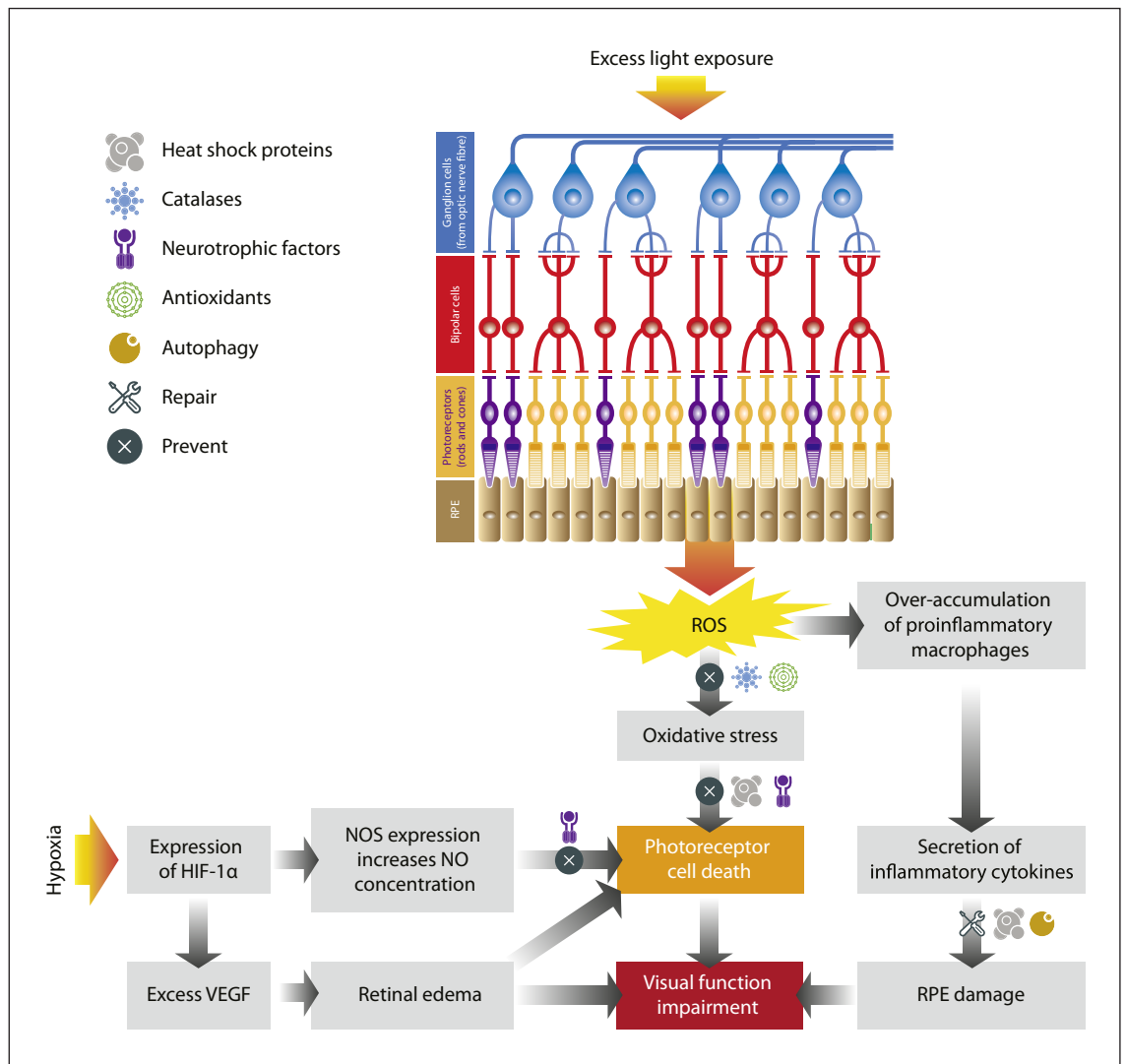


Fig. 1. Mechanisms of neural damage and neuroprotection. HIF, hypoxia inducible factor; NO, nitric oxide; NOS, nitric oxide synthase; ROS, reactive oxygen species; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

Neurotrophic Factors

Neurotrophic factors are involved in regulating the development and function of the nervous system [91] and have neuroprotective effects [84]. Ciliary neurotrophic factor (CNTF) gene therapy has been shown to confer life-long neuroprotection to photoreceptors in a mouse model [92] and can both suppress photoreceptor death and stimulate Müller glial cell proliferation [93]. However, BDNF in combination with tyrosine receptor kinase B (TrkB) gene therapy may be a more potent neuroprotector than CNTF alone; in a rat model, 76% of BDNF-treated retinal ganglion cells that had undergone TrkB gene transfer survived post-axotomy, when typi-

cally over 90% of neurons would be lost without treatment [94]. In contrast, rats with laser-induced glaucoma injected with a viral vector containing CNTF showed only 15% less retinal ganglion cell death compared to untreated rats [95]. Glial cell line-derived neurotrophic factor (GDNF) signalling has also been shown to indirectly support photoreceptor survival [96], and the anti-inflammatory effect of transduced pigment epithelium-derived factor is protective of retinal ganglion cells in the DBA/2J glaucoma mouse model [97]. As neurotrophic factors innately stimulate neuroprotection, they may be a useful starting point for treatment of retinal degeneration [98].

Stem Cell Therapy

Stem cells are able to secrete neurotrophic factors through paracrine action [99]; thus, stem cell therapy may facilitate the neuroprotection of photoreceptors. Intravitreal injections of mesenchymal stem cells engineered to secrete high levels of neurotrophic factors (BDNF, GDNF, and vascular endothelial growth factor [VEGF]) have been shown to significantly extend retinal ganglion cell survival in a rat model (69% vs. 46% with placebo, $p = 0.0005$) [99]. Furthermore, the restoration of degenerating supportive cells with stem cell-derived replacements may protect photoreceptors: insertion of human embryonic stem cell-derived RPE cells has been shown to preserve photoreceptor function long term in a rat model [100]. Similar stem cell-derived RPE cells are being trialled in humans: a phase 1 study of PF-05206388 has shown preliminary evidence for the safety and feasibility of this neuroprotective therapy in patients with AMD [101], and ongoing phase 1 and 1/2a studies are currently examining the safety, tolerability, and initial efficacy of stem cell derivatives ASP7317 and OpRegen in patients with GA [102, 103].

Catalases

Catalases are ubiquitous enzymes that catalyse the breakdown of hydrogen peroxide (a common ROS) to water and oxygen, preventing the cellular damage caused by oxidative stress [104, 105]. Previous work has shown that catalases protect rat retinas from ischemia/reperfusion damage by reducing oxidative stress [106], and nanoparticle-mediated catalases protect cultured human neurons from oxidative damage and can even restore neuronal morphology [105]. Specific to the human retina, catalases reduce the oxidative stress caused by hyperglycaemia in cultured human retinal cells [107]. Therefore, catalases may be a good neuroprotective option for both stress-associated and chronic neurodegenerative disorders [105].

Heat Shock Proteins

Heat shock proteins (HSPs) respond to cellular stress by repairing proteins and peptides and degrading irreparable proteins, thus limiting widespread cellular damage [108]. Increasing HSPB5 expression in a transgenic model of Huntington's disease confers neuroprotection through a non-cell autonomous pathway [109]. HSPB5 also plays a role in protecting the outer cells of the retina in response to severe oxidative stress [110]. Although the role of HSPs in neuroprotection and neuroinflammation is not yet fully understood, their functional role in cellular repair and association with areas of inflammation and damage may facilitate neuroprotection [111].

Autophagy

Autophagy is a process of self-degradation that removes misfolded or aggregated proteins, damaged organelles, and intracellular pathogens [112, 113]. Rapamycin, a drug that induces autophagy, has been shown to confer neuroprotection in fly and mouse models of Huntington's disease [114]. However, if autophagic recycling becomes imbalanced, it can lead to neuronal cell death; thus, careful control of autophagy is vital [112, 115]. At present, it is not clear what specific modulation of autophagy is required for neuroprotection [115]; control of autophagy could be a promising future strategy, but further studies are required to establish its role and potential for therapeutic use.

Mechanisms of Neural Damage in GA

At present, the direct causes of GA and its progression are unknown. Vision loss in patients with GA is directly related to photoreceptor dysfunction and death [116]. There are a number of mechanisms through which photoreceptors can be damaged; these are typically linked to changes in oxygenation or light-induced damage, leading to oxidative stress, proinflammatory cellular activity, and, ultimately, cell death [117–119].

Changes in Oxygenation Level

The retina is highly metabolically active, meaning that it has a great oxygen demand [120]; this renders it particularly sensitive to changes in oxygenation. Both hypoxia and hyperoxia increase the frequency of cell death in the retina, primarily in the outer nuclear layer [117]. Hypoxia in the retina induces the expression of hypoxia-inducible factor-1 α , which leads to the expression of VEGF and nitric oxide synthase [120]. VEGF production disrupts the blood-retina barrier and can lead to retinal edema [120], whereas nitric oxide synthase expression increases concentrations of nitric oxide and may directly result in cell death [120]. Furthermore, the activation of glutamate receptors in hypoxic conditions may damage the photoreceptors by initiating a biochemical cascade that increases intracellular calcium levels [120]. Since GA is associated with ischemia [121], photoreceptor damage relating to retinal ischemia due to hypoxia may be especially relevant when considering neuroprotective strategies.

Oxidative Stress

Oxidative stress is a result of an imbalance in the production and sequestering of ROS [119]. An excess of ROS can damage cellular structures, including membranes, lip-

ids, proteins, and DNA [119]. The retina is especially vulnerable to oxidative stress because of its rich polyunsaturated lipid membranes and the high metabolic rate of its neurons [76, 122, 123]. Furthermore, mitochondria, which are particularly abundant in photoreceptors, are vulnerable to damage from oxidative stress [123]; there are substantially fewer mitochondria in the RPE of patients with AMD compared with healthy individuals [124]. Oxidative stress plays a key role in a range of retinal diseases, including AMD; thus, treatment strategies that target oxidative stress in the retina may have broad applications for retinal health [125]. One ongoing phase 2 study is examining the safety and efficacy of elamipretide (a mitochondrially targeted antioxidant) in patients with GA [126]. However, the administration of antioxidants has yet to show an effect on the incidence of GA or its progression [89, 127]. That said, a recent large study (14,135 eyes) showed that dietary intake of multiple nutrients (including vitamin A, vitamin B6, β -carotene, lutein and zeaxanthin, magnesium, and copper) reduces the risk of progression from intermediate AMD to advanced AMD [128].

Proinflammatory Macrophage Activity

The immune response to oxidative damage can result in an increased presence of proinflammatory macrophages between the RPE and photoreceptor outer segments [118]; over-accumulation of macrophages between the RPE and photoreceptors is associated with the secretion of proinflammatory cytokines [129]. In a mouse model of AMD, retinal infiltration by macrophages preceded the onset of retinal damage, suggesting a causative role [118]. When exposed to proinflammatory cytokines, RPE cells express fewer than usual genes that are critically involved in the visual cycle, epithelial morphology, and phagocytosis [130]. Furthermore, senescent RPE cells upregulate AMD- and GA-associated inflammatory factors (interleukin-6 and interleukin-8), forming a cyclical pattern of damage [131–133]. The evidence linking proinflammatory macrophages to the sites of future AMD development implicates macrophage control as a potential mechanism for neuroprotection [118].

Changes in the RPE

The RPE acts as a selective barrier and vegetative regulator of the photoreceptor layer [134]; thus, changes in the RPE may have a direct effect on the health of photoreceptors. Age-related changes in the RPE, such as accumulation of lipofuscin, are associated with the pathogenesis of AMD [134]; lipofuscin is phototoxic and has been linked to oxidative changes associated with cell death [134].

Thinning of the RPE is one sign of GA [5, 9–11]; therefore, it is reasonable to assume that other changes in the RPE may play a role in GA-associated photoreceptor death. Further research is needed to establish the precise impact of RPE changes on GA.

Light-Induced Damage

Light can induce oxidative stress-mediated damage to photoreceptors. Oxidative reactions are apparent in rat retinas after 5 days of constant light exposure [135]. Light wavelengths within the visible spectrum range (415–755 nm) are associated with the highest levels of mitochondrial dysfunction in RPE cell cultures that have been modified to mimic ageing [136]. However, a meta-analysis has indicated that exposure to sunlight may not be associated with an increased risk of developing AMD in humans [137]. Although excess light can induce retinal damage, it is unlikely to be a mechanism underlying AMD or the cause of retinal dysfunction in the majority of patients.

The Rationale for Using Neuroprotection to Manage GA

Primary pathways implicated in the progression of GA are also associated with mechanisms that can damage photoreceptors, such as inflammation, oxidative stress, and blood flow regulation [70]. As neuroprotective agents can protect photoreceptors from damage and increase the survival of neural tissue by preserving neuronal structure and function [70], they are a promising disease management option for GA. Importantly, a neuroprotective mechanism may work independently from the primary disease pathomechanism of GA.

Previously Trialled Neuroprotective Therapies

Many agents, including apoptosis inhibitors, anti-inflammatory agents, neurotrophic factors, antioxidants, progesterone, ursodeoxycholic acid, and tauroursodeoxycholic acid, have been used to combat neurodegeneration in various clinical settings [85, 98, 138–143]. Although corticosteroids are not traditionally thought of as neuroprotective agents, sustained-release fluocinolone acetonide [144–146] is one example of a corticosteroid formulation that could play a neuroprotective role in retinal diseases because of its anti-inflammatory effects [146]. However, as fluocinolone is a non-specific corticosteroid, it may not sufficiently target GA lesions. Other corticosteroids in AMD have failed to improve visual

Table 1. Previously investigated neuroprotective therapies in GA, including complement inhibitors

Treatment	Endpoint(s)	Efficacy data	Safety data	Result
Fluocinolone acetamide (NCT00695318)	Change from baseline in GA lesion area	Mean growth of 2.758 mm ² and 2.562 mm ² in the dosed groups versus 2.513 mm ² and 2.599 mm ² in the sham group [144]	Between 30.00% and 71.43% of dosed patients experienced a serious AE, including ventricular tachycardia, pulmonary edema, and pneumonia aspiration, versus 17.65% in the sham group	No difference observed in GA lesion growth. Study terminated
Brimonidine (NCT02087085)	Change in GA lesion area by FAF (primary); change in BCVA; change in LLVA	Mean growth from baseline was 14.5% and 14.6% in the dosed groups versus 22.4% in the sham group (not significant). Mean BCVA loss was 10.9 letters in the dosed group versus 9.7 letters in the sham group [151]	5% discontinuation rate due to AEs. One-quarter of AEs were attributed to intravitreal injection	Small but non-significant effect on lesion growth rate. Study terminated
Tandospirone (NCT00890097)	Mean annualized lesion enlargement rate by FAF	Mean growth of 1.725 mm ² and 1.758 mm ² a year in the dosed groups versus 1.707 mm ² in the sham group [153]	Minor AEs: eye irritation (8–10%), eye pain (6–7%), and blepharitis (5–7%) [153]	No difference observed in GA lesion growth between those who received sham and those who received treatment. Study terminated
NT-501 (NCT00447954)	Change in BCVA (primary); change in ERG; change in GA lesion area; change in drusen area; change in retinal thickness	High-dose CNTF (20 mg/day) led to 96% of patients losing <3 lines of vision versus 75% of patients in the sham group (non-significant). There was a significant change in macular volume versus baseline for dosed patients versus the sham group [158]	No serious AEs reported. Instances of photopsia, miosis, and worsening of cataracts in dosed groups [158]	Non-significant improvement in number of BCVA lines lost. Phase 2 trial completed but no further results or development in GA
Eculizumab (complement inhibition, NCT00935883)	Change in GA lesion area at 26 weeks [41]	Mean lesion growth of 0.19 mm in the treatment group versus 0.15 mm in the placebo group [41]	No AEs reported in the treatment group [41]	No significant decrease observed in GA lesion growth
Lampalizumab (complement inhibition, NCT02247479)	Mean change in GA lesion area from baseline at 48 weeks [42]	Mean lesion growth of approximately 2 mm ² per year [42]	~6% of dosed patients experienced serious ocular AEs [42]	No specific benefit of lampalizumab was observed [42]
Pegcetacoplan (complement inhibition, NCT02503332)	Least square mean change in square root GA lesion size from baseline	Mean lesion growth of 0.39 mm in dosed patients versus 0.49 mm in the sham group ($p = 0.044$), but no significant effect on functional outcomes [45]	25.6% of patients receiving monthly pegcetacoplan experienced treatment-related AEs	Significant reduction in lesion growth but no significant effect on functional outcomes
Avacincaptad pegol (complement inhibition, NCT02686658)	Mean change in rate of GA growth (primary); mean change in BCVA	Mean lesion growth of 0.32 mm in dosed patients versus 0.44 mm in the sham group ($p = 0.0051$) [44]	68.7% of patients experienced treatment-emergent ocular AEs but none were considered drug related	Significant reduction in lesion growth but no significant effect on functional outcomes

AE, adverse event; BCVA, best corrected visual acuity; CNTF, ciliary neurotrophic factor; ERG, electroretinography; FAF, fundus autofluorescence; GA, geographic atrophy; LLVA, low-luminance visual acuity.

acuity [145, 147]. Several neuroprotective agents have been investigated in GA over the past decade but have typically not advanced to further trials and were largely unsuccessful (Table 1).

Brimonidine

Brimonidine is a selective α_2 -adrenergic receptor agonist that has been used in glaucoma for its intraocular pressure-lowering effects [148, 149]. It is thought that brimonidine may directly interact with α_2 receptors, leading to a reduced pathological accumulation of extracellular glutamate and preventing the death of retinal ganglion cells [149, 150]; the activation of glutamate receptors can damage photoreceptors by increasing intracellular calcium levels [120]. Brimonidine has demonstrated a small, non-significant effect on the slowing GA lesion growth; mean growth from baseline at one year was ~15% compared with ~22% in the sham group [151]. In a phase 2 trial of brimonidine for the treatment of GA, there were some discontinuations in the treatment group (~5%) due to adverse events. Although these events were not considered treatment-related, around one-quarter of all adverse events were attributed to the injection itself, highlighting the treatment burden associated with frequent intravitreal injections [151]. The lack of significant effect on GA lesion growth indicates that the specific neuroprotective mechanism of brimonidine does not sufficiently overcome the primary pathology of GA.

Tandospirone

Tandospirone [152, 153] is a 5-hydroxytryptamine-1A receptor agonist, which has been shown to protect the RPE in albino and pigmented rats [154]. Tandospirone has a lower treatment burden than intravitreal injections owing to its delivery method (eye drops) and has demonstrated only low-grade adverse events, including eye irritation (8–10%), eye pain (6–7%), and blepharitis (5–7%) [153]. However, its desirable safety profile is outweighed by its lack of efficacy in GA; no difference was observed in GA lesion growth rate between patients who received placebo and patients treated with tandospirone [153]. Furthermore, eye drops are associated with low patient compliance and can be challenging to self-administer [155]. Also, the administration of tandospirone in the form of eye drops may prevent the drug from reaching the retina in sufficient volumes to be effective [153, 156].

NT-501

NT-501 contains two human cell lines that have been genetically modified to secrete human CNTF into the vit-

reous cavity at different doses via an implanted device, providing direct retinal access [157, 158]. High doses of CNTF (20 ng/day) resulted in 96% of patients with GA losing fewer than three lines of vision (measured using BCVA) versus 75% of patients who received sham surgery; however, this difference was not statistically significant. There was a statistically significant change in macular volume versus baseline for the low- and high-dose CNTF groups as measured by optical coherence tomography ($p < 0.001$ vs. sham surgery), but it was not possible to establish whether this was due to an increase in retinal cell numbers [158]. As NT-501/CNTF is delivered via an implant, there is a reduced treatment burden for the patient as the implant is only inserted once [158]. No serious adverse events relating to the implant or surgery were reported; however, there were instances of photopsia, miosis, and worsening of pre-existing cataracts in the treated groups. Although the mechanism of action of NT-501 is appropriate for the treatment of GA, it is possible that the choice of growth factor in this trial was not suitable for GA specifically. NT-501 has been more successful in other retinal indications; in patients with macular telangiectasia, CNTF effectively slowed the progression of retinal degeneration [159].

Other Considerations

The endpoints that the aforementioned clinical trials were structured around may not have been appropriate for detecting improvements in visual function. For example, in a clinical trial of pegcetacoplan (APL-2), an anatomical reduction in GA progression was demonstrated for treated versus sham patients, but there were no efficacy differences for secondary visual endpoints such as BCVA [45]. Ensuring that trials are well designed and sufficiently powered to detect both anatomical and functional endpoints is likely to be crucial in determining the efficacy of potential new treatments for GA. This is especially relevant for treatments with neuroprotective mechanisms as they may be able to maintain visual function even when cells are anatomically dysfunctional.

Furthermore, the point at which treatment begins in clinical trials is critical for progressive diseases such as GA. As current and in-development treatments are not able to reverse photoreceptor death, the level of pre-existing atrophy in patients with advanced GA could limit treatment efficacy. This may partly explain the limited efficacy reported in previous studies of treatments for GA. The recent Classification of Atrophy Meetings (CAM) guidelines [160] may help researchers to identify

Table 2. Neuroprotective therapies currently under investigation in ocular diseases

Treatment	Indication	Intervention	Endpoints	Status
CoQ10-MINIACTIVES (NCT04038034)	Glaucoma	IOP-lowering drugs with either 100 mg b.i.d. oral administration of CoQ10-MINIACTIVES or placebo	Pattern electroretinogram amplitude at 12 months versus baseline (primary); visual field test; contrast sensitivity; peripapillary retinal nerve fibre layer thickness by OCT; macular retinal nerve fibre layer thickness by OCT	Recruiting, phase N/A
Lutein dietary supplements (NCT03932305)	Retinal detachment	Lutein vs. placebo	BCVA at 6 months versus baseline (primary); retinal anatomical changes by OCT; contrast sensitivity by Pelli-Robson chart; quality of life measures (impact of vision impairment profile)	Active, not recruiting, phase N/A
NT-501 implant (NCT02862938)	Glaucoma	NT-501 ECT implant vs. sham	Visual field (primary); retinal ganglion cell layer thickness by OCT; retinal nerve fibre layer thickness by OCT; contrast sensitivity; BCVA; optic nerve head structural change	Active, not recruiting, phase 2
ACTHAR gel (NCT01838174)	Acute optic neuritis	ACTHAR gel versus intravenous methylprednisolone	Retinal nerve fibre layer thickness (primary); frequency of retinal nerve fibre layer swelling; mood, visual function (NEI-VFQ-25) and quality of life assessment	Recruiting, phase 4

BCVA, best corrected visual acuity; b.i.d., twice daily; ECT, encapsulated cell therapy; IOP, intraocular pressure; N/A, not applicable; NEI-VFQ-25, National Eye Institute Visual Function Questionnaire (25 questions); OCT, optical coherence tomography.

patients with nascent GA (or who are at a high risk of developing GA) for inclusion in clinical trials of novel treatments and could result in improved vision outcomes for patients.

The Future Role of Effective Neuroprotection in GA: Redefining the Approach and Conclusions

GA is associated with considerable disease burden and progression. Despite this, there are currently no approved treatments to prevent the onset or delay the progression of GA. At present, a number of neuroprotective agents are under investigation in other retinal diseases (Table 2), validating the consideration of neuroprotection in GA. Although a neuroprotective mechanism could have a positive impact on the treatment landscape of GA, based on previous clinical trials (Table 1), treatment duration and efficacy need to be improved.

Future Therapeutic Approaches of Neuroprotection in GA

A treatment's duration of action will need to be considered for future therapies. GA may be similar to diseases in which chronic damage occurs gradually over time; therefore, the duration of action of previously trialled neuroprotective agents may have been too short to combat chronic and ongoing damage. Duration of action could be increased through specific treatment formula-

tions or by identifying treatments with superior ocular pharmacokinetics.

Selecting an appropriate target of action may also be critical in future clinical trials. Thinning of the RPE is a known characteristic of GA [5, 9–11]; therefore, targeting the RPE may be appropriate. However, the histopathology of GA lesions shows that the area of photoreceptor loss is much larger than the area of RPE loss [116], and micropetry has demonstrated that impairment of photoreceptor activity extends beyond the anatomical GA lesion area [161]. If photoreceptor death takes place before the RPE is lost, then the RPE may not be an ideal target for treatment, as irreversible vision loss would have already occurred. That said, the resorption of drusen and loss of the RPE are indicators of GA progression, meaning that photoreceptor death may be secondary to the presence of RPE hypopigmentation [162]. If so, the RPE could still be an ideal target for induced or transduced expression of neuroprotective proteins. One example of a potential target associated with the RPE is the DICER1 pathway. The accumulation of *Alu* RNA resulting from a DICER1 deficiency in the RPE has been implicated in GA [163–165]; a DICER1 deficit activates inflammasomes, which leads to RPE cell death via activation of caspase-8 [163, 164]. Furthermore, the inhibition of inflammasome components has been shown to prevent RPE degeneration induced by DICER1 loss [163]. As such, there is a rationale for targeting the DICER1 pathway, or another associated neuroprotective protein in the RPE, for the treatment of GA.

A number of clinical trials in GA have targeted treatment to the complement system. However, given the known ethnic variation in complement polymorphisms [37–40], such a treatment is unlikely to be equally efficacious in all populations. Accordingly, trials of complement inhibitors have shown variable success in delaying the progression of GA (Table 1) [41–43, 45].

An alternative possibility is to focus on a neuroprotective agent that directly protects the photoreceptors, which could delay vision loss despite the breakdown of the choroidal endothelium and choriocapillaris. The photoreceptors, RPE, and choriocapillaris exist in a symbiotic relationship, which breaks down in AMD [162]; detachment of the retina from the choroid leads to photoreceptor death [162]. A neuroprotective agent may prolong the survival and function of photoreceptors despite vascular damage. Although this would not treat the root cause of vision loss, a delay in photoreceptor death may be sufficient to maintain visual function for several years.

Importantly, efficacy should be measured not just using anatomical markers but also by measures of retinal sensitivity, which can be impaired even in regions of the retina that appear anatomically normal [161]. In addition to target selection, it is crucial to consider when to begin treatment; as GA is progressive and irreversible, earlier treatment is likely to preserve better visual function.

Conclusion

Neuroprotection offers a theoretical mechanism for delaying photoreceptor death; although many clinical trials of neuroprotective factors have been unsuccessful thus far, the mechanism of drug delivery, specificity of treatment and primary endpoint selection may have impacted the outcomes of these trials. Studies focusing on the effect of neurotrophic factors (or other molecules involved in their signalling cascades) could identify a neuroprotective agent with a long duration of action that delays the incidence and/or the progression of GA and, ultimately, the onset of vision loss, providing clinically meaningful benefits for patients.

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Conflict of Interest Statement

H.P.N.S. declares that he is the Editor-In-Chief of the journal *Ophthalmic Research*, and in addition declares support from the Swiss National Science Foundation, National Center of Competence in Research Molecular Systems Engineering “Molecular Systems Engineering,” the Wellcome Trust, and the Foundation Fighting Blindness Clinical Research Institute; declares membership of the Scientific Advisory Board of Astellas Institute for Regenerative Medicine; GenSight Biologics; Ionis Pharmaceuticals, Inc.; Gyroscope Therapeutics Ltd.; Janssen Research & Development, LLC (Johnson & Johnson); and Pharma Research & Early Development (pRED) of F. Hoffmann-La Roche Ltd.; Novartis Pharma AG (CORE); paid consultancy of Boehringer Ingelheim Pharma GmbH & Co; Gerson Lehrman Group; and Guidepoint; declares membership of the Data Monitoring and Safety Board/Committee of Belite Bio and ReNeuron Group Plc/Ora Inc. and the Steering Committee of Novo Nordisk (FOCUS trial); is a co-director of the Institute of Molecular and Clinical Ophthalmology Basel (IOB), which is constituted as a non-profit foundation and receives funding from the University of Basel, the University Hospital Basel, Novartis, and the government of Basel-Stadt; and is a principal investigator of grants at the USB sponsored by the following entities: IVERIC bio (Ophthotech Corporation), Kinarus AG, and Novartis Pharma AG. D.B. declares that he is a consultant with Acucela, Alimera Sciences, Allegro, Bayer, EyePoint Pharmaceuticals, ONL Therapeutics, Oxurion, and Takeda; is a consultant and researcher with Adverum, Aerpio Pharmaceuticals, Allergan, Apellis, Boehringer Ingelheim, Chengdu Kanghong, Clearside Biomedical, Genentech/Roche, Kodiak, Novartis, Regeneron, RegenXBIO, Roche, and Santen; and is a researcher with Aerie Pharmaceuticals, Gemini Therapeutics, Graybug Vision, IONIS Pharmaceuticals, Neurotech, Opthea, and Outlook Therapeutics. V.C. and A.G. are employees of Boehringer Ingelheim.

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Author Contributions

H.P.N.S., D.B., A.G., and V.C. were involved in the conceptual design of the manuscript, drafting and development, and agreement to publish.

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