Treatment of Geographic Atrophy: What's on the Horizon?

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Abstract Currently, there is no treatment to stop the progression of geographic atrophy, the advanced form of non-exudative (dry) age-related macular degeneration. Several promising therapies are being investigated in clinical trials such as antioxidants, neuroprotection agents, complement inhibitors, vascular enhancers, visual cycle modulators, and stem cell therapies. This review discusses the possible treatments that may potentially be available in the future to prevent disease progression.

Keywords Treatment of geographic atrophy · Age-related macular degeneration (AMD) · Dry AMD · Ophthalmology · Cell therapies

Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness among the elderly [1]. The non-exudative (dry) stage of AMD is the initial stage of the disease and the most common form of AMD, which can then progress to either advanced dry AMD, known as geographic atrophy (GA), or neovascular AMD. Currently, there is no approved treatment to stop the progression of dry AMD. Several mechanisms have been proposed to explain the pathogenesis of AMD, which is characterized by the loss of photoreceptors, retinal pigment epithelium and choriocapillaris in the central macula.

These pathogenic mechanisms include oxidative damage, the accumulation of toxic visual cycle byproducts such as lipofuscin, choroidal vascular insufficiency and chronic inflammation, with dysregulation of the complement system playing a major role [2]. Currently, the only published and recommended treatments to slow the progression of the disease are the use of oral supplements based on the AREDS2 [3•], cessation of smoking and a healthy diet rich in green leafy vegetables. However, several promising therapies to treat dry AMD are currently in clinical trials.

Antioxidant Drugs

Oxidative stress and the depletion of vital micronutrients may play a role in the pathogenesis of dry AMD leading to the dysfunction of RPE cells, which could accelerate the development of AMD [4–6]. The Age-Related Eye Disease Study (AREDS) was a phase III clinical trial that reduced the risk of progression to advanced AMD using oral supplementation with antioxidants and vitamins (beta-carotene, vitamin C and vitamin E), as well as minerals (zinc and copper) [7]. In the second study (known as AREDS2), omega-3 fatty acids were shown to have no added benefit, while the macular xanthophylls (lutein and zeaxanthin) was found to be a safe and effective alternative to beta-carotene, which had been linked to lung cancers in smokers and former smokers [3•].

OT-551, a synthetic lipophilic, disubstituted hydroxylamine, was developed as an antioxidant, formulated as an eye drop and used in a phase II study (NTC00306488) designed to test whether OT-551 could slow the progression of GA in eyes with AMD. The drug showed no benefit as a treatment for GA [8]. See Table 1.

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Table 1 Antioxidants

Drug	Mechanism of action	Administration	Clinical study phase	Clinical trial identifier	Sponsor	Subject condition
AREDS2	Antioxidant	Oral	Phase III	NCT00345176	National Eye Institute	Drusen
OT-551	Antioxidant	Topical	Phase II	NCT00306488	Othera Pharmaceuticals	Bilateral GA

Table 2 Neuroprotective drugs

Drug	Mechanism of action	Administration	Clinical study phase	Clinical trial identifier	Sponsor	Subject condition
Brimonidine tartrate	α -2 adrenergic receptor agonist	Intravitreal implant	Phase II	NCT00658619	Allergan	Bilateral GA
CNTF (NT-501)	Rescues photoreceptors from degeneration	Intravitreal implant (ECT)	Phase II	NCT00447954	Neurotech pharmaceuticals	GA
GSK933776	Humanized IgG1 mAb against A β N-terminus	Intravenous	Phase II	NCT01342926	GlaxoSmithKline	GA
RN6G	A β peptides antibody	Intravenous	Phase I	NCT00877032	Pfizer	GA
			Phase I	NCT01003691	Pfizer	GA
			Phase II	NCT01577381	Pfizer	GA

Neuroprotective Drugs

Neuroprotective drugs appear to act by preventing the apoptosis of viable RPE cells and photoreceptors and preserving the macular function [9]. Brimonidine tartrate is an alpha-2 adrenergic receptor agonist and is the same substance that is available as an eye drop at different concentrations for the treatment of open angle glaucoma.

Brimonidine has been shown to protect photoreceptors from retinal degeneration in animal models by stimulating the production of neurotrophic factors [10], but the precise mechanism is still unknown. Brimonidine tartrate was formulated as an intravitreal implant, and this biodegradable delivery device was used in a clinical trial in an attempt to slow the progression of GA in eyes with AMD. Since the results of the phase II trial (NCT00658619) showed equivocal results, a second study is planned.

Ciliary neurotrophic factor (CNTF/NT-501) is a cytokine member of the IL-6 family of neurotrophic cytokines that acts to preserve photoreceptor cells from retinal degeneration [11•]. CNTF receptors were identified on Müller glial membranes and on rod and cone photoreceptors [12]. A phase II study (NCT00447954) was performed to evaluate the safety and effectiveness of CNTF implants in preserving the vision of subjects with atrophic AMD. The implant of encapsulated human NTC-201 cells releasing CNTF was well tolerated and resulted in a dose-dependent increase in retinal thickness. Visual acuity was stabilized (loss of less than 15 letters) in the high-dose group (96.3 %) when compared with the low-dose (83.3 %) and sham (75 %) group, but the implant failed to slow the progression of GA.

RN6G (PF-04382923) is a humanized monoclonal antibody that binds with high affinity to amyloid- β (A β) peptides (A β -40 and A β -42), which are implicated in the pathogenesis of neurodegenerative diseases such as Alzheimer's disease. The deposition of A β could play a role in drusen biogenesis, atrophy of the RPE and the pathogenesis of AMD [13]. The intravenous infusion aims to prevent A β accumulation in the macula and remove existing A β . Two phase I clinical trials have been completed (NCT00877032/ NCT01003691), and a phase II trial is currently recruiting patients (NCT01577381) to evaluate the safety and tolerability of multiple doses of RN6G in subjects with GA due to AMD. No results have been published yet.

GSK933776 is another humanized monoclonal antibody that is directed against the N-terminal sequence of amyloid- β . A phase II multicenter, randomized, double-masked, placebo-controlled study is underway in patients with GA (NCT01342926). The primary endpoint of the study is the change in the area of GA compared with baseline. Patients are treated monthly with GSK933776 (3–6 mg/kg intravenously) or placebo and then followed for 18 months. See Table 2.

Drugs that Suppress Inflammation

The complement cascade is likely to play a role in the pathogenesis of dry AMD. Studies demonstrating an association between AMD and certain at-risk alleles of genes encoding complement proteins have led to strategies that inhibit complement activation by targeting complement components [14].

Eculizumab (Soliris) is a humanized monoclonal antibody derived from a murine anti-human C5-specific antibody [15]. By binding C5, eculizumab prevents the cleavage of C5 into C5a and C5b and prevents the downstream complement activation and formation of the membrane attack complex (MAC). Eculizumab is approved by the Food and Drug Administration (FDA) for the intravenous treatment of paroxysmal nocturnal hemoglobinuria and alpha-hemolytic uremic syndrome. A phase II clinical trial, the Complement Inhibition with Eculizumab for the Treatment of Non-exudative Macular Degeneration (COMPLETE) study (NCT00935883), evaluated the safety and efficacy of the intravenously infused drug in preventing the growth of GA and reducing drusen volume. This randomized, double-arm study enrolled 60 patients (30 patients with GA and 30 patients with drusen). A 2:1 randomization resulted in 20 patients in each cohort receiving intravenous eculizumab and 10 patients in each cohort receiving intravenous saline placebo [16•]. Eculizumab was well tolerated, but did not reduce the growth rate of GA, nor did it reduce the volume of drusen. In this study, no association was observed between the number of at-risk alleles carried by the subjects and the growth rate of GA; however, there was an association between the increase in drusen volume and the number of complement factor H at-risk alleles carried by the subjects.

LFG316 is a fully human antibody that also targets the complement factor C5. A phase I dose escalation trial has been completed (NCT01255462), and a phase II trial (NCT01527500) to evaluate the ability of LFG316 to reduce the growth of GA with monthly intravitreal injections during a 12-month period is ongoing. The estimated primary completion date is June 2014.

ARC1905 is an anti-C5 pegylated aptamer that was investigated in a randomized phase I clinical trial (NCT00950638) to evaluate the safety and tolerability of intravitreal injection in subjects with GA. This study has been completed, but results have not been released.

FCFD4514S (lampalizumab) is an antigen-binding fragment (Fab) of a humanized, monoclonal antibody directed against complement factor D, a rate-limiting enzyme involved in the activation of the alternative complement pathway. A phase I study demonstrated that the intravitreal injection of the drug in a single dose was safe and well tolerated up to a dose of 10 mg with no related ocular or systemic adverse events [17]. The results of a phase II clinical trial (NCT01602120), designed to assess the long-term safety and tolerability of repeated intravitreal injections of lampalizumab for the treatment of GA, were recently presented at the 31st Annual Meeting of the American Society of Retina Specialists in Toronto, Ontario, Canada. Subjects received intravitreal injections of lampalizumab (10 mg) either monthly or every other

month for 18 months. This randomized, multicenter, single-masked, controlled study showed a positive outcome in slowing the progression of GA in eyes injected every month with lampalizumab. The drug resulted in a 20.4 % reduction rate in the growth of GA as assessed with fundus autofluorescence at 18 months ($P < 0.1170$, statistically significant pre-specified protocol criteria). No effect was observed in the group treated every other month. In a subset of patients carrying the at-risk allele for complement factor I (CFI), which was present in 57 % of the subjects, the treatment effect increased to a 44 % reduction in growth rate ($P < 0.005$) compared with a 20.4 % reduction found in the all the monthly treated subjects at 18 months. In addition, when subjects with this CFI at-risk allele and baseline best corrected visual acuity of 20/50–20/100 were compared with sham-injected subjects, the reduction in the growth rate of GA increased to 54 % ($P < 0.005$).

Iluvien (fluocinolone acetonide) is being studied as a possible treatment for patients with bilateral GA due to AMD in a phase II clinical trial (NCT00695318). The randomized, double-masked, interventional study is evaluating the safety and efficacy of the fluocinolone acetonide intravitreal implant (0.2 and 0.5 µg/day) compared with sham injection for reducing the growth rate of GA.

Sirolimus (rapamycin), an immunosuppressive agent, is a macrolide fungicide that inhibits the mammalian target of rapamycin (mTOR) [18, 19] and is being studied in patients with GA due to AMD. A phase I/II pilot study (NCT01445548) is underway in a single center to evaluate six patients with bilateral GA. One eye of each participant was randomly assigned to receive the intravitreal injection of Sirolimus, and the other eye serves as a control. The study eye receives the drug injection at baseline and every 2 months thereafter. The outcomes will be evaluated at completion of 12 months of treatment. A multi-center, randomized, single-masked, phase II clinical trial (NCT01675947) is enrolling participants with GA to receive monthly intravitreal injection of Sirolimus or a subconjunctival sham injection during the 24-month study period. The endpoints for the two Sirolimus studies are the rate of change in the GA area and the change in visual acuity. See Table 3.

Drugs that Increase Choroidal Blood Flow

Recent studies have investigated whether a decrease in choroidal circulation may be involved in the development and progression of AMD [20, 21]. This theory presumes that the administration of vasodilators may restore the choroidal blood flow, avoiding the release of vascular endothelial growth factor (VEGF) and the consequent neovascularization.

Table 3 Drugs that suppress inflammation

Drug	Mechanism of action	Administration	Clinical study phase	Clinical trial identifier	Sponsor	Subject condition
ARC1905	Anti-C5 aptamer	Intravitreal injection	Phase I	NCT00950638	Ophthotec	GA and/or drusen
Eculizumab (Soliris)	Monoclonal antibody against C5	Intravenous	Phase II	NCT00935883	Alexion	GA or drusen
FCFD4514S (Lampalizumab)	Anti-factor D	Intravitreal injection	Phase II	NCT01602120	Genentech	GA
Fluocinolone acetonide (Iluvien)	Suppression of inflammation glucocorticoid-mediated	Intravitreal injection	Phase II	NCT00695318	Alimera Sciences	GA
LFG316	Human antibody against C5	Intravitreal injection	Phase II	NCT01527500	Novartis	GA
Sirolimus	mTOR inhibitor	Intravitreal injection	Phase I/II	NCT01445548	National Eye Institute	Bilateral GA
			Phase II	NCT01675947	National Eye Institute	GA

Table 4 Vascular enhancer

Drug	Mechanism of action	Administration	Clinical study phase	Clinical trial identifier	Sponsor	Subject condition
MC-1101	Choroidal blood flow modulator	Topical	Phase II/III	NCT01601483	MacuCLEAR	Non-exudative AMD

MC-1101 is a topically administered eye drop developed to increase choroidal blood flow. Originally developed as an antihypertensive drug, the mechanism of action is associated with the generation of nitric oxide (NO) to produce vasodilation. A phase I clinical trial (NCT01013376) has shown that MC-1101 is safe and well tolerated in humans. A phase II/III trial (NCT01601483) is currently ongoing to evaluate the efficacy and safety of topical 1 % MC-1101 administered three times a day. The study is a randomized, double-masked investigation of patients with mild to moderate non-exudative AMD, and visual function is the primary outcome after 2 years. See Table 4.

Visual Cycle Modulators

The goal of visual cycle modulation is to reduce the accumulation of toxic fluorophores in the RPE and prevent the loss of the RPE and photoreceptors. These fluorophores include lipofuscin and its major component, A2E (*N*-retinylidene-*N*-retinylethanolamine), a cytotoxin generated from retinoid by-products of the visual cycle [14, 22].

ACU-4429 (emixustat hydrochloride) is a non-retinoid molecule developed to be a selective visual cycle modulator that targets rod cells. The oral administrations of ACU-4429 is intended to reduce the accumulation of toxic products (A2E) by binding and inhibiting the activity of the

isomerase known as the RPE-specific 65-kDa protein (RPE65), thereby preventing the conversion of all-trans-retinol to 11-cis-retinol [2]. However, the side effects of reducing the levels of 11-cis retinol include difficulties with dim light vision, dark adaptation and dyschromotopia. A phase I trial (NCT00942240) with healthy volunteers compared oral emixustat with placebo and demonstrated that all the doses of emixustat (5, 10, 20, 30 and 40 mg) were well tolerated, and no serious adverse effects were identified [23, 24]. The visual symptoms presented during the study were transient. A subsequent phase II study (NCT01002950) enrolled 72 subjects with GA and has been completed, but no results have been published as yet. A large phase II/III trial (NCT01802866) was started in February 2013 and is designed to compare the efficacy and safety of ACU-4429 with placebo and to determine whether the drug reduces the rate of progression of GA in subjects with dry AMD.

Fenretinide [*N*-(4-hydroxyphenyl)-retinamide] is a synthetic drug that binds to retinol-binding protein 4 (RBP4), displaces all-trans retinol from RBP4 and disrupts the retinol-dependent RBP4–transthyretin (TTR) interaction, thereby preventing transport of all-trans-retinol in the circulation [25]. In an animal study, fenretinide reduced the bisretinoid production and accumulation of lipofuscin and A2E in the RPE [26]. A randomized, double-masked, phase II study (NCT00429936) comparing the safety and efficacy

Table 5 Visual cycle modulators

Drug	Mechanism of action	Administration	Clinical study phase	Clinical trial identifier	Sponsor	Subject condition
ACU-4429 (emixustat hydrochloride)	Non-retinoid molecule/ inhibits activity of RPE65	Oral	Phase II Phase II/III	NTC01002950 NCT01802866	Acucela Acucela	GA GA
Fenretinide	Retinol analog (inhibits binding of retinol to RBP)	Oral	Phase II	NCT00429936	Sirion therapeutics	GA

Table 6 Cell therapies

Drug	Mechanism of action	Administration	Clinical study phase	Clinical trial identifier	Sponsor	Subject condition
HuCNS-SC cells	HuCNS-SC cells transplantation into subretinal space	Stem cell implant	Phase I/II	NCT01632527	Stem cells	GA
MA09-hRPE cells	Transplantation of hESC-derived RPE cells	Stem cell implant	Phase I/II Phase I/II	NCT01344993 NCT01674829	Advanced cell technology CHA Bio and Diostech	GA GA

CNTF ciliary neurotrophic factor, *ECT* encapsulated cell technology, *IgG1* immunoglobulin 1, *mAb* monoclonal antibody, *Aβ* amyloid-β, *C5* complement factor 5, *mTOR* mammalian target of rapamycin, *RPE* retinal pigment epithelium, *HuCNS-SC* human neural stem cells, *hESC* human embryonic stem cell

of fenretinide with placebo has been completed. Subjects with GA received oral placebo or fenretinide (100–300 mg) daily for 24 months. The study showed that fenretinide was safe and found to produce dose-dependent reversible reduction in serum RBP-retinol that could be related to a trend in reducing the growth rates of GA [27]. However, no definitive treatment benefit was recognized. Potential side effects include night blindness and dry eye. See Table 5.

Cell Therapies

Cell therapy is also emerging as a treatment approach for dry AMD [28–30]. Stem cell therapy is being investigated as a way to replace damaged RPE cells, prevent progression of the disease and the deterioration of the photoreceptors, and sustain visual function [31].

MA09-hRPE, RPE cells derived from embryonic stem cells, have been transplanted to treat patients with dry AMD and Stargardt disease. Two clinical trials (NCT01344993 and NCT01674829) are currently underway to evaluate the safety and tolerability of subretinal transplantation of the human embryonic stem cell MA09-hRPE in eyes with GA secondary to AMD and Stargardt disease.

A phase I/II study of subretinal transplantation of human central nervous system (HuCNS-SC) stem cells (NCT01632527) in eyes with GA is currently underway and designed to evaluate the safety and efficacy of this treatment. The trial consists of two cohorts. Cohort I will

include four subjects who will undergo transplant with 200,000 cells followed by four subjects who will undergo transplant with 1 million cells. Cohort II will include eight subjects who will undergo transplant with 1 million cells. See Table 6.

Summary

Several drugs are under investigation for the treatment of dry AMD. Antioxidants, neuroprotectors, complement inhibitors, vascular enhancers, visual cycle modulators and stem cells are some of the promising strategies that have been tried or are in clinical trials. To date, only the AREDS2 has convincingly demonstrated a benefit in slowing the progression of dry AMD to neovascular AMD, while the complement inhibitor lampalizumab has shown some preliminary evidence that it might slow the growth rate of GA. Results from several ongoing trials should be available in 2014.

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