Treatment of Dry Age-Related Macular Degeneration

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Abstract

A number of different approaches are under development for treating nonexudative manifestations of age-related macular degeneration (AMD). Some interventions target specific pathways that are believed to play a role in AMD pathogenesis, e.g. oxidative damage, lipofuscin accumulation, chronic inflammation (including complement activation), extracellular matrix changes (e.g. β-amyloid accumulation), impaired choroidal blood flow, and apoptosis. In principle, these therapies can be combined ('combination therapy'), which may lead to synergistic effects that include better visual outcome, less likelihood for 'escape' (i.e. drug resistance), and less frequent treatment.

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Introduction

A number of treatments for nonexudative age-related macular degeneration (AMD) are under study. Several processes have been implicated in the pathogenesis of AMD, including oxidative damage, accumulation of toxic visual cycle products, chronic inflammation (including complement activation), and choroidal vascular insufficiency [1]. In this chapter we discuss interventions that target these processes to prevent the progression from early- to late-stage nonexudative AMD.

Antioxidants

The Age-Related Eye Disease Study (AREDS, NCT00594672) showed that the use of a daily dose of 80 mg zinc oxide, 2 mg cupric oxide, 15 mg β-carotene, 500 mg vitamin C, and 400 IU vitamin E in patients with extensive intermediate drusen, at least one large (≥125 μm) druse, noncentral geographic atrophy (GA) in 1 or both eyes, choroidal neovascularization in 1 eye, or visual acu-

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ity ≤20/40 in 1 eye due to AMD reduces the risk of moderate visual loss by 19% (during a 5-year follow-up period) [2]. Because the use of β-carotene increases the risk of lung cancer in smokers (or among persons who have stopped smoking within the previous 8 years) [3, 4], patients who smoke should not use this formulation unless they have stopped smoking at least 8 years previously. In general, it may be wise to ask the patient's internist to approve the use of these supplements due to these and other concerns (e.g. use of high-dose zinc in patients with a history of prostate cancer or copper in patients with a history of dementia). The AREDS did not show a statistically significant benefit of the formulation for either the development of new GA or for involvement of the fovea in eyes with preexisting GA. In part, this result may be due to the paucity of patients with GA who were enrolled in the study.

Cysteine is an important antioxidant involved in the regulation of apoptosis and immune function. Moriarty-Craige et al. [5] conducted an ancillary study in which a subset of AREDS subjects at two sites were studied at two time points, an average of 1.7 and 6.7 years after enrollment, to determine whether antioxidant supplements alter the plasma glutathione and/or cysteine redox potential in AMD patients. The AREDS antioxidant supplements reduced oxidation of cysteine to cystine but had no effect on glutathione. The authors suggested that because cysteine is important for cell growth, apoptosis, and immune function, the beneficial effect of antioxidant supplementation on progression to advanced AMD may be explained, in part, by its effect on the ratio of cysteine/cystine and/or its effect on cysteine availability. Brantley et al. [6] carried out a study to determine whether short-term AREDS antioxidant and zinc supplementation affects biomarkers of oxidative stress, possibly serving as a predictor of their efficacy. Short-term AREDS supplementation significantly lowered mean plasma levels of cystine in participants on a regulated diet. The authors concluded that a 5-day course of antioxidant and zinc supplements can modify plasma levels of cystine, suggesting that this oxidative stress biomarker could help predict how likely an individual is to benefit from the AREDS supplementation.

AREDS2 (NCT00345176), a randomized, double-masked, multicenter phase III clinical trial, was designed to determine whether adding lutein and zeaxanthin, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), or both to the AREDS formulation decreases the risk of developing advanced AMD and to evaluate the effect of eliminating β-carotene, lowering the zinc dose (to 25 mg), or both in the AREDS formulation [7]. Participants were randomized to receive lutein (10 mg) + zeaxanthin (2 mg), DHA (350 mg) + EPA (650 mg), lutein + zeaxanthin, and DHA + EPA, or placebo. All participants were also asked to either take the original AREDS formulation or accept a secondary randomization to four variations of the AREDS formulation, including elimination of β-carotene, lowering of zinc dose, or both [7]. A comparison with placebo in the primary analyses demonstrated no statistically significant reduction in the progression to advanced AMD: lutein + zeaxanthin (hazard ratio, HR, 0.90; 98.7% CI, 0.76–1.07; p = 0.12), DHA + EPA (HR, 0.97; 98.7% CI, 0.82–1.16; p = 0.70), and lutein + zeaxanthin and DHA + EPA (HR, 0.89; 98.7% CI, 0.75–1.06; p = 0.10). There was no apparent effect of β-carotene elimination or lower-dose zinc on the progression to advanced AMD [7]. More lung cancers were noted in the β-carotene versus the no β-carotene group: 23 (2.0%) versus 11 (0.9%; nominal p = 0.04), mostly in former smokers [7]. The authors concluded that the addition of lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation in primary analyses did not further reduce the risk of progression to advanced AMD. However, because of the potential of increased incidence of lung cancer in former smokers, lutein + zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation [7]. In an exploratory analysis of lutein/zeaxanthin versus no lutein/zeaxanthin [8], the HR of the development of late AMD was 0.90 (95% CI, 0.82–0.99; p = 0.04). An exploratory analyses of a direct comparison of lutein/zeaxanthin with β-carotene showed HR of 0.82 (95% CI, 0.69–0.96; p = 0.02) for the development of late AMD, 0.78 (95% CI, 0.64–0.94; p = 0.01) for the development of neovascular AMD and 0.94 (95% CI, 0.70–1.26; p = 0.67) for the development of central GA [8]. In analyses restricted to eyes with bilateral large drusen at baseline, the direct comparison of lutein/zeaxanthin with β-carotene showed HR of 0.76 (95% CI, 0.61–0.96; p = 0.02) for the progression to late AMD, 0.65 (95% CI, 0.49–0.85; p = 0.002) for neovascular AMD and 0.98 (95% CI, 0.69–1.39; p = 0.91) for central GA [8]. Thus, replacing β-carotene with lutein and zeaxanthin may not only be safer but might also provide greater protection against the development of late AMD, specifically neovascular complications and not GA.

Carotenoids, especially lutein and zeaxanthin, comprise the macular pigment. The primary direct antioxidant function of carotenoids is to scavenge singlet oxygen, but they also quench the triplet state of photosensitizers and delay the peroxidation of membrane

phospholipids [9, 10]. Factors associated with increased risk for AMD and increased risk for low macular pigment density include age, cigarette smoking, female gender, light iris color, and increasing lens density [11–14], but not all clinical studies confirm the association between low macular pigment density and increased risk for AMD [15]. Two postmortem studies revealed decreased retinal lutein and zeaxanthin in AMD eyes versus controls [16, 17]. Increasing age and advanced AMD in the fellow eye have been associated with a relative absence of macular pigment [18]. The Intervention Trial in Early Age-related Macular Degeneration (I-TEAM; NCT01694680) is an ongoing, randomized, placebo-controlled multicenter study aimed to assess the effect of 1 year of daily consumption of a lutein-enriched egg beverage on the maintenance of visual function in subjects with early signs of AMD (i.e. AREDS categories 2 or 3).

Visual Cycle Inhibitors

Excessive lipofuscin accumulation in the retinal pigment epithelium (RPE) may play an important role in AMD pathogenesis [19]. In RPE cells, the main source of lipofuscin is probably partially degraded components of phagocytized outer segments [20]. Components of lipofuscin arise from the visual cycle.

The visual cycle involves the following sequence of events. In vertebrate photoreceptors, light causes isomerization of 11-*cis*-retinylidene to all-*trans*-retinylidene followed by the release of all-*trans*-retinal from the opsin binding pocket and its reduction to all-*trans*-retinol [21]. ABCA4, an ATP-binding cassette transporter present in the outer segment of rods and cones, transports N-retinylidene-phosphatidylethanolamine from the outer segment discs to the photoreceptor cytoplasm [22, 23]. Retinol dehydrogenases in the inner and outer segments reduce all-*trans*-retinal to all-*trans*-retinol [24, 25]. Vitamin A (all-*trans*-retinol) diffuses to RPE where it is esterified by lecithin/retinol acyltransferase to all-*trans*-retinyl esters and is stored in retinosomes [26, 27]. All-*trans*-retinyl esters are isomerized to 11-*cis*-retinol in a reaction involving RPE65 [28–30]. Next, 11-*cis*-retinol is reduced to 11-*cis*-retinal [31, 32] which then diffuses across the extracellular space to photoreceptors and recombines with rod and cone opsin proteins to regenerate visual pigments.

Within the outer segment discs, ethanolamine can combine with two retinaldehyde molecules to form N-retinylidene-N-retinylethanolamine (A2E); A2E is a major fluorophore in RPE lipofuscin [33]. Inhibition of the visual cycle, by blocking all-*trans*-retinol RPE uptake or by blocking the formation of 11-*cis*-retinal, should reduce the production of lipofuscin and A2E [34, 35].

Retinol-binding protein (RBP) has a high-affinity binding site for all-*trans*-retinol. Retinol binding to RBP creates a high-affinity binding site for transthyretin. N-(4-hydroxyphenyl) retinamide (fenretinide, Sirion Therapeutics, Tampa, Fla., USA) displaces all-*trans*-retinol from RBP and prevents the interaction of RPB with transthyretin. In the absence of transthyretin binding, the RBP-fenretinide complex is excreted in urine (due to its relatively small size). Thus, fenretinide treatment causes a dose-dependent, reversible reduction in circulating RBP and retinol. Due to the unique requirement of the eye for retinol delivered by RBP, during chronic fenretinide administration levels of retinol within the eye will be reduced while other extrahepatic tissues obtain retinol from alternative sources. Fenretinide reduces lipofuscin and A2E accumulation in the RPE of ABCA4$^{-/-}$ mice and causes modest delays in dark adaptation [34]. However, data from preclinical models indicate that other mechanisms may be involved in all-*trans*-retinol delivery to the eye, and restriction of dietary vitamin A may be important in achieving a reduction of ocular all-*trans*-retinol levels even when using fenretinide [36, 37].

The efficacy of fenretinide (100 and 300 mg daily, orally) to slow lesion growth in GA patients was examined in a 2-year, placebo-controlled, double-masked trial (NCT00429936) [38]. Fenretinide treatment produced dose-dependent reversible reductions in serum RBP-retinol that were associated with trends in reduced GA growth rates. Patients in the 300-mg group who achieved serum retinol levels of ≤1 μM (≤2 mg/dl RBP), for example, showed a reduction in the yearly lesion growth rate compared with subjects in the placebo group (1.70 vs. 2.03 mm/year, respectively; p = 0.1848). Fenretinide treatment also reduced, in a nondose-dependent manner, the incidence of choroidal neovascularization (about 45% reduction in incidence rate in the combined fenretinide groups vs. placebo; p = 0.0606) [38].

Isotretinoin or 13-*cis*-retinoic acid (Accutane; Hoffmann-La Roche, Inc., Nutley, N.J., USA) is used for the treatment of acne. This visual cycle modulator is associated with a high incidence of nyctalopia because it inhibits the conversion of all-*trans*-retinyl esters in retinosomes to 11-*cis*-retinol, as well as the conversion of 11-*cis*-retinol to 11-*cis*-retinal by retinol dehydrogenase. As expected, isotretinoin inhibits lipofuscin formation in ABCA4$^{-/-}$ mice [39, 40].

Emixustat (ACU-4429; Acucela, Seattle, Wash., USA) is a nonretinoid that inhibits the conversion of all-*trans*-retinyl ester to 11-*cis*-retinol via the blockade of RPE-specific 65-kDa protein (RPE65) or another protein needed for isomerization of all-*trans*-retinol [41]. ACU-4429 also reduces RPE lipofuscin and A2E accumulation in mice and reduces retinal neovascularization in a model of retinopathy of prematurity [42]. A phase I study (NCT00942240) demonstrated that oral administration of ACU-4429 produced a dose-dependent inhibition of the electroretinogram b-wave, was well tolerated up to 75 mg, and demonstrated linear pharmacokinetics across doses [43]. Adverse events were dose dependent, mild and visual in nature (dyschromatopsia and alteration in dark adaptation), transient, and resolved within a few days after cessation of therapy [43]. A phase II study (NCT01002950) to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ACU-4429 in subjects with GA has been completed, but no results have been published as yet. A phase IIb/III (NCT01802866) multicenter, randomized, double-masked study to determine whether ACU-4429 reduces the rate of progression of GA compared with placebo in subjects with dry AMD is in progress.

Anti-Inflammatory Agents

AMD is associated with chronic inflammation in the region of the RPE, Bruch's membrane, and the choroid [44–46]. Corticosteroids have antiangiogenic and anti-inflammatory effects. Iluvien (Alimera Sciences, Alpharetta, Ga., USA) is an injectable, nonerodible, intravitreal implant containing 190 µg of the corticosteroid fluocinolone acetonide. A phase II study (NCT00695318) was recently completed after the recruitment of 40 patients with bilateral GA who were randomized to a high (0.5 µg/day) or low (0.2 µg/day) dose of Iluvien, with the fellow eye used as a control. The primary outcome of the study was the rate of GA enlargement in treated versus untreated eyes. The results of the study are unpublished at this time.

Drusen and GA are associated with mutations in components of the complement pathway, which is part of the innate immune system [45, 47]. Mutations in components of the complement pathway modulate the risk of developing AMD and include the following loci: complement factor H (CFH), complement component 2 (C2), complement factor B (CFB), complement component 3 (C3), and complement factor I (CFI) [48–61]. The alter-

native complement pathway is continuously activated in the fluid phase, and tissue surfaces require continuous complement inhibition to prevent spontaneous autologous cell injury [62, 63]. Oxidative stress can compromise the regulation of the complement system by RPE cells [64–66].

C3 inhibition might be effective at blocking complement activation that arises from many different mutations in the complement cascade (thus targeting a relatively large population of AMD patients). This degree of complement inhibition, however, may create risks such as an increased risk of injection-associated endophthalmitis [67–69]. POT-4 (Potentia Pharmaceuticals, Louisville, Ky., USA, and Alcon, Hünenberg, Switzerland) is a C3 inhibitor that binds C3 and prevents its proteolysis to C3a and C3b. It is administered by intravitreal injection, and gel-like deposits form in the vitreous when POT-4 is injected at high concentrations, thus providing a sustained-release delivery system that lasts for approximately 6 months. A phase I study of POT-4 in dry AMD eyes was completed successfully without safety concerns (NCT00473928).

With the inhibition of C5, terminal complement activity is blocked, but proximal complement functions (e.g. C3a anaphylatoxin production, C3b opsonization, immune complex and apoptotic body clearance) remain intact. ARC1905 (Ophthotech Corp., Princeton, N.J., USA) is an anti-C5 aptamer administered by intravitreal injection. A phase I clinical trial (NCT00950638) in patients with nonexudative (as well as exudative) complications of AMD has been completed, but the results are unpublished. Eculizumab (Soliris; Alexon Pharmaceuticals, Cheshire, Conn., USA) is a humanized monoclonal antibody that blocks C5, is administered intravenously and is approved by the US Food and Drug Administration (FDA) for the treatment of paroxysmal nocturnal hemoglobinuria. A phase II placebo-controlled study (NCT00935883) to assess the effect on the rate of GA progression and change in drusen volume showed that intravenous eculizumab was well tolerated in AMD patients but did not decrease the growth rate of GA significantly [70].

LFG316 (Novartis Pharmaceuticals, Whippany, N.J., USA) is an antibody directed against C5 and is administered intravitreally. The phase I study (NCT01255462) to assess the safety and tolerability of intravitreal LFG316 in patients with advanced AMD, GA or choroidal new vessels was completed, and a phase II study to evaluate the efficacy of 6 successive monthly doses on the growth of GA is underway (NCT01527500). Factor D is the rate-

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limiting enzyme in the activation of the alternative complement pathway. Genetic polymorphisms as well as hyperactivity of the alternative complement pathway have been implicated in the development of AMD, including GA [71]. Factor D inhibitors, e.g. BCX1470 (Alcon, Fort Worth, Tex., USA) and lampalizumab (FCFD4514S; Genentech/Roche, San Francisco, Calif., USA) block the activation of the alternative complement pathway while preserving the activation of the classical and lectin pathways, thus possibly reducing the risk of infectious complications associated with treatment. Lampalizumab is a monoclonal F_{ab} fragment directed against factor D. A phase II clinical trial (NCT01602120, MAHALO) involving 143 patients with bilateral GA assessed the effects of monthly versus bimonthly intravitreal lampalizumab injections of 5 mg, 10 mg, or sham on the change in the GA area during an 18-month period, using fundus autofluorescence images to identify areas of GA. Preliminary results indicate a 20.4% reduction in the rate of GA enlargement at the 18-month follow-up (p < 0.1179, statistically significant per prespecified protocol criteria) with efficacy observed beginning at month 6 [72]. In GA patients with CFI mutations treated monthly with lampalizumab, the GA progression rate was decreased by 44% (p < 0.005) at 18 months. In this study, 57% of the patients were positive for CFI mutations. If these results are confirmed in a phase III trial, they may mean that complement inhibition is useful even at a late stage of AMD. In addition, patients will require genetic testing to assess their likelihood to respond to the therapy.

Sirolimus (rapamycin; MacuSight/Santen, Union City, Calif., USA) is a macrolide fungicide that blocks the mammalian target of rapamycin, a protein kinase that regulates proliferation, motility, survival, and protein synthesis. Sirolimus has anti-inflammatory, antiangiogenic and antifibrotic effects. A single-center, open-label phase II trial (NCT00766649) enrolled 11 participants with bilateral GA; 8 participants completed 24 months of follow-up [73]. Sirolimus (440 μg) was administered every 3 months as a subconjunctival injection in only 1 randomly assigned eye/participant for 24 months. Fellow eyes served as untreated controls. The primary efficacy outcome measure was the change in the total GA area at 24 months. At month 24, the mean GA area increased by 54.5 and 39.7% in the study and fellow eyes, respectively (p = 0.41), whereas mean visual acuity decreased by 21.0 and 3.0 letters in the study and fellow eyes, respectively (p = 0.03). Substantial differences in mean change in the drusen area, central retinal thickness and macular sensitivity were not detected for all analysis time points up to 24 months.

Glatiramer acetate (Copaxone; TEVA, Petah Tikva, Israel) induces glatiramer acetate-specific suppressor T cells and downregulates inflammatory cytokines. It can be administered subcutaneously and has been studied in a phase II/III clinical trial in patients with drusen (NCT00466076). A small, controlled study demonstrated efficacy after 12 weeks of subcutaneous injections: 4 patients were treated with weekly subcutaneous injections of Copaxone (20 mg), and all 8 study eyes showed a decrease in the total drusen area [74].

Drusen vesicles contain fibrillar amyloid composed, in part, of amyloid-β [75, 76]. Amyloid-β induces the production of interleukin-1β and tumor necrosis factor-α by macrophages and microglia, which can cause an increased expression of CFB in RPE and may contribute to AMD progression [77]. RN6G (PF-4382923; Pfizer, New York, N.Y., USA) is a humanized monoclonal antibody that targets the C-termini of amyloid-β_{40} and amyloid-β_{42}. Treatment with intravenous RN6G is intended to prevent the accumulation and cytotoxic effects of amyloid-β_{40} and amyloid-β_{42} by removing amyloid from the tissue compartment through mass action kinetics. Beneficial effects were documented in a mouse model of AMD [78]. Phase I and II clinical trials have been completed successfully to evaluate the safety of the treatment in patients with advanced dry AMD (NCT01003691, NCT01577381). We are not aware of plans to carry out phase III studies of RN6G. GlaxoSmithKline has successfully completed a phase I study of intravenous GSK933776, an intravenously administered humanized monoclonal antibody directed against amyloid-β. This antibody reduces the accumulation of amyloid-β and C3a deposition in Bruch's membrane of $cfh^{-/-}$ mice [79]. A phase II study (NCT01342926) is underway.

Drugs That Increase Choroidal Blood Flow

Choroidal blood flow decreases with age, probably due to a decrease in choriocapillaris diameter and density [80]. In addition, decreased choroidal blood flow is correlated positively with fundus findings associated with an increased risk of choroidal neovascularization (i.e. drusen, pigmentary changes) [81]. The administration of vasodilators may improve choroidal blood flow, possibly delaying the progression of nonexudative as well as exudative manifestations of late AMD [82]. A pilot study (NCT01013376) investigating the safety of MC-1101, an eye drop developed to increase choroidal blood flow by the generation of nitric oxide to induce vasodilation, has

demonstrated that it is safe and well tolerated in humans [83]. Increased choroidal blood volume and velocity were demonstrated in treated AMD eyes. MC-1101 is also anti-inflammatory and an antioxidant. The active ingredient of MC-1101 is already used as an approved oral antihypertensive agent. A randomized, double-masked phase II/III trial (NCT01601483) investigating patients with mild-to-moderate nonexudative AMD is ongoing to evaluate the efficacy and safety (visual function is the primary outcome after 2 years) of topical 1% MC-1101 administered 3 times a day.

Neuroprotective Therapy

Apoptosis, programmed cell death, has an important homeostatic function; however, apoptosis has been implicated in the pathogenesis of AMD [84]. Neuroprotective drugs are intended to preserve macular function by preventing apoptosis of viable RPE cells and photoreceptors.

Ciliary neurotrophic factor (CNTF), a member of the IL-6 family of neuropoietic cytokines, delays the loss of photoreceptors in animal models of retina degenerative disease [85]. CNTF can be delivered using encapsulated cell technology (ECT) [86]. Using ECT, genetically modified RPE that overexpresses CNTF is housed in a semipermeable capsule with small pores that permit CNTF to escape into the vitreous cavity and protect the allogeneic RPE cells from immune rejection. The ECT device is implanted in the vitreous cavity and comprises a sustained CNTF delivery system.

Zhang et al. [87] reported the results of a 1-year, phase II randomized, double-masked, controlled dose-ranging study involving the use of CNTF-ECT (NT-501 implant; Neurotech, Lincoln, R.I., USA) to treat GA. A total of 51 individuals were randomly assigned to receive high-dose (n = 27) or low-dose (n = 12) implants or sham surgery (n = 12). At the 12-month follow-up, 96.3% of patients in the high-dose NT-501-treated cohort lost <15 letters (ETDRS) versus 75% of patients in the sham group (p = 0.078). No increase in vision occurred, and no serious adverse events were reported. The trend in visual stabilization at 12 months was preceded (at 4 months) by a dose-dependent, statistically significant increase in retinal thickness (p < 0.001 and p = 0.013 for the high- and low-dose cohorts, respectively) by optical coherence tomography. CNTF-induced increased retinal thickness has been reported in laboratory animals with retinitis pigmentosa-like conditions [88, 89]. In mice, this thickness change reflects, in part, increased photoreceptor nuclear size and increased amounts of euchromatin, and in rcd-1 dogs it reflects increased photoreceptor nuclear size as well as swelling of photoreceptors and/or Müller cell processes, with expansion of the outer limiting membrane towards the RPE.

Brimonidine is an α-2 adrenergic receptor agonist that is approved by the US FDA for the treatment of glaucoma. Brimonidine protects retinal ganglion cells, bipolar cells, and photoreceptors from degeneration in several models of experimental injury, including retinal ischemia, partial optic nerve crush, ocular hypertension, and retinal phototoxicity [90–92]. The proposed mechanisms of neuroprotection include the following: increased expression of basic fibroblast growth factor, a cytokine that delays apoptosis; upregulation of endogenous production of trophic factors such as brain-derived neurotrophic factor in retinal ganglion cells; stabilization of mitochondrial transmembrane potential under conditions of oxidative stress, and suppression of the accumulation of glutamate causing neuronal cell death [92, 93]. Brimonidine is delivered by a sustained-release biodegradable implant (Allergan, Irvine, Calif., USA) that is injected into the vitreous through a 22-gauge needle with the same applicator system used to deliver dexamethasone (Ozurdex; Allergan). A randomized, double-masked, dose-response, sham-controlled phase II study of the safety and efficacy of brimonidine intravitreal implants in patients with GA has been completed (NCT00658619). In this 2-year follow-up study, 119 patients with bilateral GA and visual acuity between 20/40 and 20/320 were randomized to receive the brimonidine delivery system containing either 200 or 400 μg of drug or sham treatment. The patients received the drug or sham treatment in 1 eye and sham treatment in the fellow eye on day 1 and a repeat of the assigned treatment and sham treatment at month 6. The primary outcome measure was the change of GA lesion area in the study eye from baseline to month 12. The results of this trial showed equivocal results. A second study is planned.

Stem Cell Therapy

Stem cell-derived RPE and photoreceptors have been shown to rescue the retina, replace lost retinal neurons, and restore vision in various animal models of retinal degenerative disease (reviewed in Zarbin [94]). Stem cells also provide a unique opportunity to create in vitro models of retinal diseases such as AMD [95]. The pathology

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and pathophysiology of AMD indicate that RPE transplants may prevent disease progression through the replacement of dead and dying RPE [96–98]. Because of their unlimited proliferative potential, stem cells may be an ideal source of tissue from which large numbers of therapeutic cells may be derived for transplantation purposes [99]. Induced pluripotent stem cell-derived human RPE has been shown to rescue the retina in animal models of retinal degeneration involving RPE mutations that preclude normal phagocytic function [100]. In addition, stem cell-derived RPE produces neurotrophic factors that should support photoreceptor survival [101]. Schwartz et al. [102] reported the results of embryonic stem cell-derived RPE transplantation in patients with AMD and Stargardt disease. This report is preliminary and involves a small number of patients with a short follow-up, but promising visual results were reported in 1 patient with Stargardt disease whose vision improved from hand motions to 20/800 in the treated eye during the first 3 months after subretinal transplantation of the stem cell-derived RPE. It is not clear if the basis of the improved vision was due to the replacement of native RPE or simply to a rescue effect mediated by neurotrophic factor production from the transplanted cells.

Other stem cell studies are in early phases of development. A phase I/II study of subretinal transplantation of human central nervous system stem cells (NCT01632527) in eyes with GA, for example, is currently underway and designed to evaluate the safety and efficacy of this treatment. At this time it is clear that, with certain precautions, stem cells can be produced en masse safely and that they can be induced to differentiate into ocular cells with the potential for replacement and rescue therapy. Challenges to successful stem cell therapy for degenerative retinal disease include the following: the abnormal microenvironment of the diseased eye, which can compromise cell survival and differentiation [103]; synaptic rewiring that accompanies retinal degeneration and which may compromise replacement strategies [104]; maintenance of functional phenotype over time; immune rejection, particularly for embryonic stem cell-derived RPE [105], and transplantation of 'healthy' cells, particularly for induced pluripotent stem cell-derived RPE from AMD donors.

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