Emerging Treatments for Dry AMD

A number of early clinical trials are under way.

BY DAVID S. BOYER, MD

With the advent of several efficacious pharmacologic treatments for exudative age-related macular degeneration (AMD) in the past decade, it is disheartening to consider that to date there is only one proven treatment for dry AMD, and that is a nutritional supplement. The formula used in the Age-Related Eye Diseases Study (AREDS), with a high-dose combination of vitamin C, vitamin E, beta-carotene, and zinc, lowered the risk of developing advanced stages of dry AMD and reduced visual loss in people at risk for the disease.

The AREDS formula did not, however, prevent geographic atrophy (GA) from forming or progressing. A follow-up study, AREDS2 is assessing a modified formula containing lutein, zeaxanthin, and omega-3 polyunsaturated fatty acids, to see whether this combination can further slow the progression of vision loss from dry AMD.

A number of proposed pharmacologic treatments for dry AMD have not stood up to scrutiny in clinical trials. Laser to drusen, as applied in the Complications of AMD Prevention Trial (CAPT), did not demonstrate clinically significant reduction of vision loss in patients with large drusen. Rheopheresis showed no effect in a U.S. clinical trial. Anecortave acetate (Alcon Laboratories), after undergoing extensive study, was found to be ineffective in reducing the chance of developing wet AMD in high-risk eyes. OT-551 (Othera Pharmaceuticals), an antioxidant vitamin, showed a trend toward maintaining visual acuity but no statistically significant effect on GA.

Despite these disappointments, some promising treatment strategies are emerging. These strategies fall into two categories: the prevention of photoreceptor and retinal pigment epithelium (RPE) loss through (1) neuroprotection, (2) the reduction of toxic byproduct accumulation, or (3) visual cycle modification; or the suppression of inflammation. This article reviews the status of some of these emerging strategies and possible future treatments for dry AMD.

NEUROPROTECTION

Three drugs with neuroprotective properties are being investigated as treatments for dry AMD: an implanted encapsulated cell technology (NT-501, Neurotech); intravitreal brimonidine tartrate (Allergan); and topical tandospirone (AL-8309B, Alcon).

NT-501 is a ciliary neurotrophic factor (CNTF), a neuroprotective cytokine that prevents photoreceptor degeneration. It is one of the most powerful retinal neuroprotective agents known. CNTF prevents the loss of the outer nuclear layer. In an animal model, eyes implanted with polymer membrane capsules that secreted CNTF had a marked increase in the thickness of the outer nuclear layer compared with fellow untreated eyes.

NT-501, an encapsulated cell technology device implanted through a small incision and sutured to the sclera, contains modified RPE cells that secrete CNTF in a controlled, sustained fashion. The device was evaluated in a phase 2 double-masked, sham-controlled study in 51 patients randomized 2:1:1; 24 patients received a high-dose implant, 12 patients received a low-dose implant, and 12 received placebo in a sham procedure. The end-point was visual acuity at 12 months. Secondary endpoints included macular thickness/volume on optical coherence tomography (OCT) and lesion size.

Results at 1 year showed a nonstatistically significant trend toward stabilization of visual acuity (Figure 1) in the high-dose group. In the subgroup of patients with initial good visual acuity, the high dose appeared to maintain that good vision (Figure 2). There was, however, no difference in progression of GA with the implant compared with sham.

Brimonidine tartrate, an alpha-2 adrenergic receptor agonist, has been shown to be neuroprotective of retinal ganglion cells, bipolar cells, and photoreceptors in numerous animal models of nerve insult including ischemia, ocular hypertension, phototoxicity, and partial optic nerve crush. When administered in a chronic release form, brimonidine seems to protect photoreceptors from blue light damage in a dose-responsive manner.

The manufacturer has formulated brimonidine for sustained delivery in the system used to deliver dexamethasone for posterior uveitis and retinal vein occlusions (Ozurdex, Allergan). In this sustained-release for-
Reduction of the accumulation of toxic byproducts is an encouraging approach to treatment, not only for GA but also for patients with drusen. Two substances using this strategy are being assessed: subcutaneous glatiramer acetate (Copaxone, Teva Pharmaceutical Industries) and intravenous RN6G (PF-4382923, Pfizer), an anti-amyloid beta (Aβ) antibody.

Why target Aβ for treatment of dry AMD? Johnson et al reported that Aβ is found in drusen.10 Deposition of Aβ may be an important component of local inflammatory events that contribute to the damage in AMD, and if we can reduce the amount of Aβ in the retina, perhaps we can reduce damage to the RPE and the pathogenesis of AMD.

Glatiramer acetate appears to reduce Aβ-induced retinal microglial cytotoxicity and allow a neuroprotective phenotype of microglia to form.11 The drug has been approved by the US Food and Drug Administration (FDA) for treatment of multiple sclerosis. Recently, Landa and colleagues12 found that, after 12 weeks of subcutaneous treatment, glatiramer shrank or eliminated more drusen (27.8%) than did sham treatment (6.8%; \( P=0.008 \)).

RN6G is a humanized monoclonal antibody against both Aβ40 and Aβ42. Administered intravenously, it binds and sequesters Aβ species in the retinal periphery, reducing the pool of toxic species in the macula and preventing the accumulation of Aβ40 and Aβ42, which have been implicated in neurodegenerative disorders. Pfizer has completed a phase 1 safety trial of the compound. A phase 2 study is planned, in which 45 subjects with dry AMD will be treated with escalating doses monthly for 6 months. In a transgenic mouse model of dry AMD, treated eyes showed less structural and functional change than those receiving vehicle alone.

VISUAL CYCLE MODULATORS

Visual cycle modulators have received considerable attention in ophthalmology lately. There are two in development for treatment of dry AMD, oral fenretinide (RT-101; ReVision Therapeutics) and oral ACU-4429 (Acucela). Visual cycle modulation essentially “slows down” the activity of the rods and reduces the metabolic load on the cones. It is hoped that, in doing this, these compounds can slow the deterioration that accompanies aging, reduce the accumulation of toxic fluorophores (A2E) and lipofuscin, and prevent the loss of photoreceptors and RPE cells.

Holz and coworkers13 showed that excessive lipofuscin and A2E accumulation is related to the progression of GA. A2E causes destabilization of cell membranes, interferes with cell metabolism, and triggers downstream activation of complement.

ACU-4429 is a small molecule, given orally, that acts selectively on the rod photoreceptors. Rods are the major source of A2E, and 90% of the photoreceptor cells are rods. This compound inhibits Rpe65 in the visual cycle and thereby reduces the buildup of 11-cis retinol and slows down the rod visual cycle (Figure 3).
ACU-4429 has demonstrated efficacy in multiple pre-clinical models, including aged animal models, a light-damage model (Figure 4), and a retinopathy of prematurity model.\textsuperscript{14–16} It reduces the buildup of toxic byproducts of the visual cycle.

A phase 2 trial, called ENVISION-CLARITY, is planned, a randomized, double-masked, placebo-controlled, multicenter study of the safety and efficacy of ACU-4429 in patients with dry AMD and GA. Three escalating dose levels, and up to two additional dose levels, will be evaluated, with each escalation reviewed and approved by a data monitoring committee. Patients will receive once-daily dosing over 3 months with treatment or placebo. Planned enrollment is 84 patients.

Fenretinide is a derivative of vitamin A that possesses apoptotic, antiangiogenic, and antiinflammatory properties. It has been investigated for potential use as a treatment for cancer, rheumatoid arthritis, and other diseases and has a proven safety profile in more than 30 large clinical studies with more than 8,000 patient years of human exposure. Adverse events are typical of retinoids and decrease over time.

Fenretinide inhibits uptake of all-trans-retinol by the RPE. Its mechanism of action is attributed to a structural property that allows fenretinide to compete with retinol for binding to the retinol binding protein (RBP). Although retinol and fenretinide are similar chemically, fenretinide has a side chain that prevents interaction with transthyretin (TTR). In the absence of TTR binding, the RBP-fenretinide complex is excreted in urine due to its relatively small size.

The immediate effect of fenretinide treatment, a reduction in circulating RBP and retinol, is dose-dependent and reversible. With chronic fenretinide administration, levels of retinol within the eye are dramatically reduced, while other tissues will obtain retinol from alternate sources.\textsuperscript{17}

A phase 2 study of fenretinide has been completed.\textsuperscript{18}

This double-masked, randomized, placebo-controlled, multicenter trial included 246 patients with GA within 500 µm of the fovea randomized to placebo, 100 mg, and 300 mg fenretinide.

The manufacturer of the drug was changed about 1 year into the trial. There were differences in particle size and bioavailability between the two lots of drugs, which seemed to have an effect on outcomes.

In a planned interim analysis when the last patient enrolled reached 1 year follow-up, it was found that patients who enrolled earlier in the trial and received the original formulation of the drug had sustained reduction of RBP, which correlated with reductions in GA lesion growth.

In addition to its effect on GA, fenretinide was also found to reduce the incidence of choroidal neovascularization in both treatment arms. Treatment was generally well tolerated with anticipated side effects, particularly affecting night driving ability. ReVision Therapeutics plans to initiate a phase 3 trial program this year.

**SUPPRESSION OF INFLAMMATION**

Suppression of inflammation in dry AMD is being investigated with a number of approaches, including glucocorticoid treatment and complement inhibition.

**Glucocorticoids.** An extended-release fluocinolone acetonide (FA) implant (Iluvien, Alimera Sciences) that is FDA-approved for the treatment of posterior noninfectious uveitis is being investigated in a phase 2 clinical trial in 40 patients with bilateral GA.\textsuperscript{19} The primary outcome measure will be the difference in GA enlargement between the treated eyes and the untreated fellow eyes. The results of this trial have not been released.

**Complement inhibition.** The complement system is part of the innate immune system. It helps to defend the body from infection and to modulate immune and inflammatory responses. The alternative pathway of complement has...
attracted the most interest among ophthalmic investigators. Anderson and colleagues\(^2\) identified C5 and the membrane attack complex in human donor eyes and concluded that the membrane attack pathway of the complement cascade may be implicated in the process of drusen formation.

A number of compounds are being evaluated for complement inhibition in dry AMD. Among them, two promising candidates are POT-4 (Potentia Pharmaceuticals) for inhibition of C3 and eculizumab (Soliris, Alexion Pharmaceuticals) for inhibition of C5.

POT-4 is given as an intravitreal injection in a high dose (1.05 mg), and it precipitates out in the posterior segment and can be seen on ultrasound B-scan. Clotted together in the vitreous cavity, it does not seem to affect vision and dissolves over 3 to 4 months. In a phase 1 study,\(^2\) a single injection of POT-4 was given in doses from 1 µg up to 1.05 mg in 27 patients. Preliminary results indicate that intravitreal POT-4 is safe and support the continued investigation of the efficacy of POT-4 for the treatment of both wet and dry AMD in larger randomized clinical trials.

Eculizumab is a complement inhibitor that is approved by the FDA for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). It is a humanized immunoglobulin-G antibody against C5. Administered by intravenous infusion, it prevents lysis of the RBC. C5 inhibition has some potential advantages over C3 inhibition:

1. It blocks only terminal complement activity, so the proximal functions of complement remain intact.
2. It blocks only terminal complement activity, so the proximal functions of complement remain intact.

The efficacy and safety of eculizumab for the treatment of dry AMD are being evaluated in the investigator-sponsored COMPLETE study at the Bascom Palmer Eye Institute.\(^2\) Patients will receive 6 months of therapy, then be followed every 3 months. The results of this study have not been released.

Important information is still to be learned about the use of complement inhibition in dry AMD. Will this therapy require life-long inhibition? What are the therapeutic benefits vs the risks of inhibition? Will it work for wet AMD as well as dry AMD? Where in the pathway should we block complement? Should it be blocked locally or systemically?

**CONCLUSION**

One of the difficulties in dry AMD research is that it is a uniquely human disease with no good animal models. Despite this, valiant research efforts continue at many centers around the country and around the world.

Current treatment strategies being investigated for treatment of dry AMD target preservation of photoreceptors and RPE, prevention of oxidative damage, and suppression of inflammation. Many clinical early trials are under way, and it is to be hoped that within the next year some of them will yield promising results and point the way toward future therapies.

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18. Phase 2b data suggest ReVision’s oral fenretinide (RT-101) slows lesion growth, preserves vision and reduces incidence of neovascularization in geographic atrophy patients [press release]. Chicago, IL; ReVision Therapeutics; October 18, 2010.