

## Clinical Update

TOOLS AND TECHNIQUES

## RETINA

# Dry AMD: Under Attack on Four Fronts

BY MIRIAM KARMEI, CONTRIBUTING WRITER

**I**nvestigational efforts to treat dry AMD are flowering as much as in any branch of eye research. “We are very fortunate that there is such interest in the treatment of geographic atrophy associated with AMD,” said Emily Y. Chew, MD, deputy director of the division of epidemiology and clinical research at the National Eye Institute. “This is very important as this is a leading cause of blindness, with an unprecedented increase over the next decades as the aging population grows.”

The research, however, has yet to bear fruit. “Dry AMD is very complicated. It is a disease that has to be attacked by multiple methods,” said Paul S. Bernstein, MD, PhD, professor of ophthalmology and visual sciences at the University of Utah in Salt Lake City. The current studies focus on chronic inflammation, the damage of oxidation and the toxins of everyday ocular physiology. Accordingly, researchers are trying to modulate the normal visual cycle, block the complement system, protect photoreceptors and introduce nutrients that benefit the eye.

Despite their differences, these approaches all attempt to prevent damage to the retina by targeting aspects of what is believed to be the early process of the disease. “Everybody is working on the same common pathway, but it’s a different step on the pathway,” said Ryo Kubota, MD, PhD, a molecular biologist and former clinical ophthalmologist who is now chief executive

officer of Acucela in Bothell, Wash.

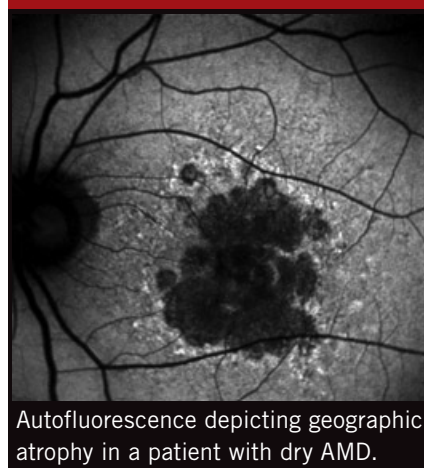
What follows is a look at four current therapeutic concepts. All are in human trials, but none has completed the rigors of large-scale studies, and that’s important to keep in mind, said Dr. Chew. “It would be best not to be judging their efficacy at this early stage with such small sample sizes and short study duration. Interpretation of structural changes without accompanying measures of function should be conducted with caution.”

### Visual Cycle Modulation

The human visual cycle is configured such that by day the eye uses its cones, and by night its rods. The rods, however, continue working even during the day. During exposure to light, they generate by-products such as lipofuscin—and a major component of lipofuscin called A2E—which accumulate in the retinal pigment epithelial cells with age and have been linked to macular degeneration and degenerative retinal diseases. “Lipofuscin is a classic hallmark of aging, like a wrinkle in the skin,” Dr. Kubota said.

**ACU-4429** (Acucela) can modulate—in this case, slow down—the visual cycle, according to Acucela researchers. ACU-4429 is an oral drug that targets the rod system by inhibiting a key enzyme. This inhibition of the rod system does not affect the cones but reduces the rate at which A2E and lipofuscin accumulate in the RPE, said Dr. Kubota. “A2E can create a lot of free radicals and can trigger inflammation.

### Blinding Geography



Autofluorescence depicting geographic atrophy in a patient with dry AMD.

It can be linked to all the hypotheses out there. So we think the dry AMD process can be slowed down.”

In preclinical studies conducted by Acucela, ACU-4429 slowed the rod visual cycle, decreasing the accumulation of A2E. And in an animal model, the drug reduced A2E and lipofuscin and protected photoreceptors from acute light damage.

In phase 1 human trials, daily, single-dose oral administration of ACU-4429 appeared to be safe and well-tolerated in healthy volunteers aged 55 to 80.<sup>1</sup> Phase 2, beginning later this year, will test multiple doses in patients with geographic atrophy. Researchers hope to determine the level of slowdown that preserves retinal health without significantly reducing dark adaptation, Dr. Kubota said. “We don’t want to shut it down 100 percent.”

**Fenretinide** (Sirion Therapeutics) is

another agent that reduces the production of lipofuscin and A2E by modifying the visual cycle. Fenretinide is an oral vitamin A binding protein antagonist. Interim phase 2 results of a two-year, multicenter study of 225 patients were presented at the last ARVO meeting. Patients had been randomized to placebo, or 300-mg or 100-mg doses of fenretinide daily. In the group of patients on 300 mg a day, the inhibition was the most marked: The growth of lesions was 22.7 percent at 18 months, compared with 41.6 percent in the placebo group. Slower growth, but not as remarkable, was also observed in the 100-mg group. The trend was evident as early as six months.<sup>2</sup> “Our results are the first time anyone has modified the progress of geographic atrophy,” said Roger Vogel, MD, chief medical officer of Sirion Therapeutics in Tampa, Fla. The phase 3 trial of fenretinide, which has received an FDA “fast-track” designation, could begin mid-2010.

### Complement Inhibition

The complement system is at the core of many chronic inflammatory processes and can result in cell membrane disruption. Some gene variants encoding components of the complement system have been linked to a predisposition for AMD. Complement-mediated tissue damage has also been linked to other eye pathologies, including glaucoma, uveitis and multiple sclerosis.

**POT-4** (Potentia Pharmaceuticals), a derivative of the cyclic peptide compstatin, is designed to inhibit complement component C3 from participating in the complement activation cascade. Unchecked, C3 can lead to local inflammation, tissue damage and upregulation of angiogenic factors such as vascular endothelial growth factor (VEGF).

Ophthalmologists already have at their disposal ranibizumab (Lucentis) to inhibit VEGF. But POT-4 works upstream from that growth factor, and thus could nip the degenerative process in the bud, said Pascal D. Deschatelets, PhD, CEO of Potentia Pharmaceuticals in Louisville, Ky. “We

believe POT-4 acts at a point that is closer to the root cause of the disease,” Dr. Deschatelets said.

POT-4 is not intended to replace Lucentis but might be used for Lucentis nonresponders, or before the need for Lucentis arises, said Dr. Deschatelets. “We think POT-4 might be good at addressing dry AMD and geographic atrophy, while Lucentis treats CNV.” He expects that a single intravitreal injection of POT-4 may provide sustained therapeutic ocular levels of the drug for several months. Last May, Potentia reported that the 27 patients in the phase 1 open-label study responded well at all doses tested.

While phase 1 patients had very advanced wet AMD, phase 2, expected to begin early 2010, should involve both wet and dry patients, Dr. Deschatelets said.

### Neuroprotection

Ciliary neurotrophic factor (CNTF) is a neuroprotectant cytokine under study for the treatment of certain neurodegenerative diseases, including amyotrophic lateral sclerosis and Huntington’s disease.

**NT-501 intraocular implant** (Neurotech) delivers human cells that have been genetically modified to secrete CNTF. Phase 2 trial results reported by the company showed that NT-501 substantially slowed the loss of vision in patients with geographic atrophy. A high dose was shown to stabilize best-corrected visual acuity at 12 months, with 96.3 percent of treated-patients losing fewer than three lines of vision, vs. 75 percent of patients in the sham group. But no increase in BCVA was detected in any of the 51 subjects, whether on high or low dose.<sup>3</sup>

**OT-551** (Othera Pharmaceuticals) is topically dosed to treat geographic atrophy by reducing oxidative stress and disease-induced inflammation. In addition, it may have a neuroprotective effect. In animal models, OT-551 demonstrated a dose-dependent effect on photoreceptor activity. In multiple species, the small, lipophilic molecule readily penetrated the cornea.

A phase 2, double-masked, dose-

ranging study, OMEGA, is under way to determine whether treatment with OT-551 reduces progression of GA, as well as to assess safety and measure changes in BCVA. Last April, a Data and Safety Monitoring Committee reviewed the 12-month results and determined that the study should continue to its predetermined primary endpoint at 24 months, said Paul Sternberg Jr., MD, professor and chairman of ophthalmology at Vanderbilt University in Nashville, Tenn., and chairman of the OMEGA study. The committee did not recommend release of the 12-month data, he added.

### Carotenoid Supplementation

Certain nutrients may be protective against dry AMD, according to the landmark finding of the AREDS trial. Now researchers are modifying the AREDS formula by eliminating beta-carotene, decreasing the zinc, and adding omega-3 fatty acids and two xanthophylls—lutein and zeaxanthin. The xanthophylls, which are carotenoids found in many fruits and vegetables, are central to ocular physiology.

**Lutein and zeaxanthin** are found in the macula at concentrations 100- to 1,000-fold higher than anywhere else in the body, according to Dr. Bernstein. In the retina, they may play an important protective role against macular degeneration through antioxidant and light-screening mechanisms. Dr. Bernstein, whose clinic is an approved AREDS2 site, is trying to identify and characterize the binding proteins that are responsible for uptake and stabilization of lutein and zeaxanthin in the macula.

When he started working in this field, studies were linking dietary consumption of these compounds to protection against AMD. “I wanted to understand why the macula was going out of its way to concentrate these compounds. I wanted to understand how and why it was getting there.”

In 2004, he identified a zeaxanthin binding protein, GSTP1. Last spring he identified the lutein binding protein, HR-LBP. Zeaxanthin appears to act as a light-screening compound, while

lutein may work as an antioxidant.

In the meantime, treating AMD through diet or supplements isn't simple, Dr. Bernstein said. "Some people can take large amounts of these supplements, but the amount in the eye doesn't change because their binding proteins are saturated." In others, the effect is dramatic, he said.

### **What Now for Patients Losing Vision?**

To a patient worried about losing vision to geographic atrophy, research is still just research. But with fenretinide on a fast track, and the first AREDS trial having a positive outcome, there is a bridge to hope for these patients. Definitive AREDS2 recommendations are four or five years off, but Dr. Bernstein sees no problem with patients taking the supplements as there is very little downside and no reported toxicity. "There is accumulating evidence from both basic and clinical science that lutein and zeaxanthin are going to be important in helping to prevent AMD in later life."

Dr. Chew views the situation with measured optimism. "We are certainly living in an exciting period of clinical research for age-related macular degeneration, and we look forward to reviewing these studies when they complete the phase 3 randomized, controlled trials. For the sake of the affected individuals participating in these trials, we should all be mindful of the equipoise that needs to be maintained to complete the studies."

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1 ACU-4429 results presented at ARVO, 2009, Fort Lauderdale, Fla.

2 Fenretinide results presented at ARVO, 2009, Fort Lauderdale, Fla.

3 NT-501 results presented at ARVO, 2009, Fort Lauderdale, Fla.

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*Dr. Bernstein is a consultant and research grantee of Kemin Health, a consultant for Kalsec and a scientific advisory board member for Science Based Health. Dr. Chew has no financial interests. Dr. Deschatelets is CEO of Potentia Pharmaceuticals. Dr. Kubota is president and CEO of Acucela. Dr. Vogel is chief medical officer of Sirion Therapeutics. Dr. Sternberg receives grant support from Othera.*