Developments in Therapy for Dry AMD

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Last year, for the Retina Today issue focused on age-related macular degeneration (AMD), I contributed an article on drugs in the pipeline for treatment of wet AMD (see Developments in Therapy for Wet AMD in the May/June 2013 Retina Today). The present article is meant as a complement, describing drug candidates in the pipeline for treatment of dry AMD. As will be seen, this is an area that currently represents a serious unmet medical need for patients with both types of AMD, wet and dry.

RECAP AND UPDATE

In my previous article, I noted that a gap has developed between the labeling of drugs available to ophthalmologists for treatment of neovascular AMD (what we should do) and their actual use in clinical practice (what we are doing). (For more on trends in current injection practice, see Anti-VEGF Maintenance Therapy for Neovascular AMD on page 63 of this issue.)

For potential ways to close that gap, last year’s article described 3 alternative strategies beyond the injection of available anti-VEGF agents. Drugs using 1 of those 3 strategies that were in various stages of clinical investigation for treatment of wet AMD were described. Those strategies are:

• Finding a better anti-VEGF agent. Two products currently in clinical investigation are of interest here. One is ESBA (Alcon), a humanized single-chain antibody fragment and a pan-VEGF-A inhibitor; a phase 2 trial (OSPREY) comparing the frequency of injections of ESBA and aflibercept was recently completed, and results should be forthcoming. The other is DARPin (designed ankyrin repeat protein; Allergan), a novel class of small molecule that can be designed to bind to any receptor; the REACH study, with a complex design in 3 stages, is ongoing with stage 1 complete.

• Finding a better anti-VEGF delivery system. There are 3 strategies being investigated in this area, 2 involving gene therapy. Genzyme and Avalanche are each developing delivery methods for the tyrosine kinase inhibitor sFLT-1, a chimeric protein that binds to VEGF receptors. Genzyme’s approach uses a viral vector, delivered via intravitreal injection, while Avalanche uses a subretinal injection following a vitrectomy. Phase 1 studies of each have been completed. Another approach is Neurotech’s encapsulated cell technology, essentially a protein factory implanted in the posterior segment. This technology is now in its third generation, with a phase 3 study expected to begin this year.

• Exploring combination treatment. An inhibitor of platelet-derived growth factor, called Fovista (E10030, Ophthotech) is being investigated as a combination therapy with an anti-VEGF agent. In a large phase 2 study, the combination therapy met the prespecified primary endpoint of superiority over anti-VEGF monotherapy, demonstrating a 62% additional benefit with classic dose-response profiles at all time points. There was consistency of results in all prespecified subanalyses, with marked reduction of vision loss.

COMMON PATHWAY

All of these therapies show promise and remain under investigation for the treatment of wet AMD, but in the meantime therapeutic options for dry AMD are lacking. This is unfortunate because it is becoming increasingly apparent that dry AMD and the development of geographic atrophy (GA) represent the final common pathway of all AMD. It is no longer a matter of dry or wet AMD, but rather this final common pathway of the development of GA, the natural history of the disease, that leads to irreversible vision loss.

That is to say, even in patients being successfully treated for the neovascular component of their AMD, vision loss will continue to occur through the progression of dry AMD and GA. Fortunately, early stage clinical trials are under way evaluating 2 promising approaches to dry AMD therapy.

In the past decade-plus, researchers have determined that a high level of metabolism occurs in the retinal pigment epithelium (RPE) photoreceptor complex, especially in the macula region. This metabolism results in the production of large quantities of vitamin A toxins, which in a healthy eye are ingested and recycled by the RPE. With age, however, an overburdened RPE cannot support the metabolic requirements of the photoreceptor cells, and this leads to
photoreceptor cell death and permanent vision loss. This is the mechanism that causes dry AMD and GA.\(^1\)

Dietary supplementation with the AREDS formulation of antioxidant vitamins, beta carotene, and zinc has been shown to reduce the risk of progression to advanced AMD by 25% at 5 years.\(^2\) Stem-cell based regenerative medicine may hold promise in the future. For the present, however, 2 strategies to try to prevent dry AMD progression are being investigated clinically: visual cycle modulation to prevent photoreceptor and RPE loss, and complement inhibition to suppress inflammation.

**VISUAL CYCLE MODULATION**

Visual cycle modulation is the process of reducing visual chromophore biosynthesis through the inhibition of key enzymes or proteins in the visual cycle. It is believed that this approach will be effective to reduce metabolic activity of rod and cone photoreceptors and also to decrease the production of toxic vitamin A byproducts and lipofuscin. Reducing the accumulation of toxic vitamin A byproducts, such as A2E, may be particularly relevant for the treatment of GA, as this compound has been implicated in accelerating the accumulation of lipofuscin and causing damage to cell membranes through free radical formation and various inflammatory processes.\(^3\)

Emixustat HCl (ACU-4429, Acucela) is an orally administered, nonretinoid small molecule visual cycle modulator that has been designed to specifically inhibit the activity of the visual cycle isomerase (RPE65) to reduce the rate of vitamin A processing in the visual cycle. RPE65 has been explored as a potential therapeutic target in preclinical models since the early 2000s.\(^4,6\) Data from these studies has demonstrated that inhibition of RPE65 can halt the accumulation of A2E, reduce the metabolic rate of photoreceptors, and protect the retina from light damage.

Emixustat has been studied for safety across 5 phase 1 studies in 125 healthy humans, over a treatment duration of up to 14 days, in whom it was generally well-tolerated with mostly mild ocular adverse events, typically related to the mechanism of action of the drug. Electroretinogram (ERG) was used in a single-dose phase 1 study, and a dose-related pharmacologic response was seen, with suppression of rod photoreceptor cell function. The suppression was reversible within 9 days after cessation of drug administration.

A phase 2a randomized, double-masked, placebo-controlled, multicenter ENVISION-CLARITY trial evaluated escalating doses of emixustat in patients with GA associated with dry AMD. This trial investigating the safety, tolerability, and pharmacodynamics of emixustat, has been completed, and results are currently undergoing manuscript review.

A phase 2b/3 placebo-controlled 2-year study, SEATTLE, is ongoing, evaluating the long-term safety and efficacy of emixustat in slowing lesion growth in patients with GA. Patients are randomized to 1 of 3 doses or placebo, and there is an up-titration design for the highest dose, 10 mg. This is to evaluate whether achieving the high dose in a stepwise manner will potentially mitigate initial drug-related ocular adverse events.

**COMPLEMENT INHIBITION**

The complement system is part of the innate immune system. It has 3 main activation pathways, the classical, alternative, and lectin pathways. When 1 of these pathways is activated by various molecular structures, a series of endogenous proteins acts as inhibitors to prevent excessive activation and protect host cells. The complement system also defends the body from infection and modulates immune and inflammatory responses.

The complement system came into the ophthalmic lexicon when it was realized, about a decade ago, that complement was present in drusen. Work by Anderson and colleagues implicated the membrane attack pathway of the complement cascade in the process of drusen formation.\(^7\)

Lampalizumab, also known as anti-factor D (Genentech), is a selective inhibitor of the alternative complement pathway. Lampalizumab is a fragment antigen binding of a humanized monoclonal antibody that inhibits complement factor D, blocking activation of the alternative complement pathway while preserving the host-defense response. The scientific rationale for this drug is that genetic polymorphisms in multiple alternative complement pathway loci are associated with the risk of AMD. Complement factor D is a rate-limiting enzyme in the alternative pathway.

A phase 2 study, MAHALO, has been completed, and results were presented at last year’s Retina Subspecialty Day at the American Academy of Ophthalmology Annual Meeting.\(^8\) Patients were randomly assigned to 1 of 4 arms (1:2:1:2), receiving either sham or a lampalizumab 10-mg injection, either every month or every other month. The 2 sham arms were pooled for data analysis.

Enrolled patients had to have at least 1 disc area of GA secondary to AMD without choroidal neovascularization. The primary endpoint was mean change in GA area from baseline on fundus autofluorescence at 18 months. Secondary endpoints included change in visual acuity. Also part of the design was an exploratory analysis to evaluate the relationship between specific genetic polymorphisms associated with GA disease characteristics and patient response to lampalizumab.

MAHALO was the first study to demonstrate a positive treatment effect with a complement inhibitor in GA. At month 18, the MAHALO all-comers population showed a 20.4% reduction in GA area. Of note, the exploratory analysis showed that 57% of samples collected were positive for...
the complement factor I biomarker (CFI+). Patients who received monthly injections and were CFI+ showed a 44% reduction, and those who received every-other-month injection and were CFI+ showed an 18% reduction. The results suggest the CFI biomarker is both prognostic for GA progression and predictive for lampalizumab treatment response, although the sample size was small.

The safety profile of lampalizumab was acceptable, with no endophthalmitis, no deaths, and no ocular serious adverse events caused by the study drug.

CONCLUSIONS
Dry AMD is difficult to study because it is a uniquely human disease with no good animal models. Early clinical trials using 2 strategies are under way. One strategy is to prevent RPE and photoreceptor loss, and the most encouraging approach to this goal is visual cycle modulation. Another strategy is suppression of inflammation, and here complement inhibition is the most promising avenue.

Although neovascular AMD receives much of the attention in research and in clinical practice, dry AMD is probably the most important type of AMD because it appears to be a final common pathway of the disease. With the aging of the population, dry AMD is truly an epidemic, and there is no other unmet need in retina that requires more attention.

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