

Fenretinide Treatment of Geographic Atrophy in Dry AMD: Preliminary Results

BY ALEXANDER M. EATON, MD

Fenretinide is a synthetic derivative of vitamin A and its characteristics have been investigated in numerous disease states. It has been shown to have chemoprotective, apoptotic, antiinflammatory, and antiangiogenic properties, and its side effects include mild to moderate drying of mucosal membranes, and a delay in dark adaptation.

The pathogenesis of age-related macular degeneration (AMD) is multifactorial, including, in addition to inflammation and angiogenesis, the accumulation in the retina of lipofuscin and retinol (vitamin A)-derived toxins, such as A2E. Sparrow and colleagues¹ have shown that high concentrations of A2E and related toxins compromise cellular processes in the retinal pigment epithelium (RPE), leading to cell death. RPE cell death in turn leads to photoreceptor cell death.

Fenretinide has demonstrated its ability to reduce the accumulation of lipofuscin and retinol-derived toxins in a Stargardt disease animal model.² Fenretinide reduces circulating levels of retinol and its carrier protein, retinol binding protein (RBP). Because A2E and related toxins are derived from retinol, reduction in circulating RBP-retinol leads to reduced levels of retinol-derived toxins in the eye.

PHASE 2 PROOF OF CONCEPT CLINICAL TRIAL

These findings formed the rationale for a phase 2 proof-of-concept study to determine whether fenretinide (RT-101, ReVision Therapeutics) is efficacious in the treatment of geographic atrophy (GA) in patients with dry AMD.³

In this phase 2, multicenter, double-masked, placebo-controlled study, 246 enrolled subjects were randomized equally to a once-daily oral dose of 100 mg fenretinide, 300 mg fenretinide, or placebo. Subjects included were patients older than 50 years of age whose visual acuity ranged from 20/20 to 20/100 and who had an aggregated GA lesion area of 2 to 8 disc areas. Patients with choroidal neovascularization (CNV) were excluded, as were those with inflammatory disease of the retina, glaucoma, diabetic retinopathy, and other vascular diseases.

The primary efficacy outcome measure was the size of the GA lesion. Secondary endpoints included visual acuity, CNV emergence during the study, and safety endpoints. Evaluations were performed at 1, 3, 6, 12, 18, and 24 months.

INTERIM RESULTS

The average age in the study population was 80 years, with age equally distributed among the three groups. Baseline visual acuity was also fairly equally distributed among the three groups. Mean lesion size was slightly larger in the fenretinide groups but well within the standard deviation.

Results for the first 30% of patients enrolled in the trial are discussed below.³ The study was not sufficiently powered for the results in this interim report to achieve statistical significance.

A trend toward a dose-dependent response to fenretinide was seen regarding growth of the GA lesion area. The effect was manifest at 6 months and increased at 12 months and 18 months. By 24 months, the 300 mg fenretinide group

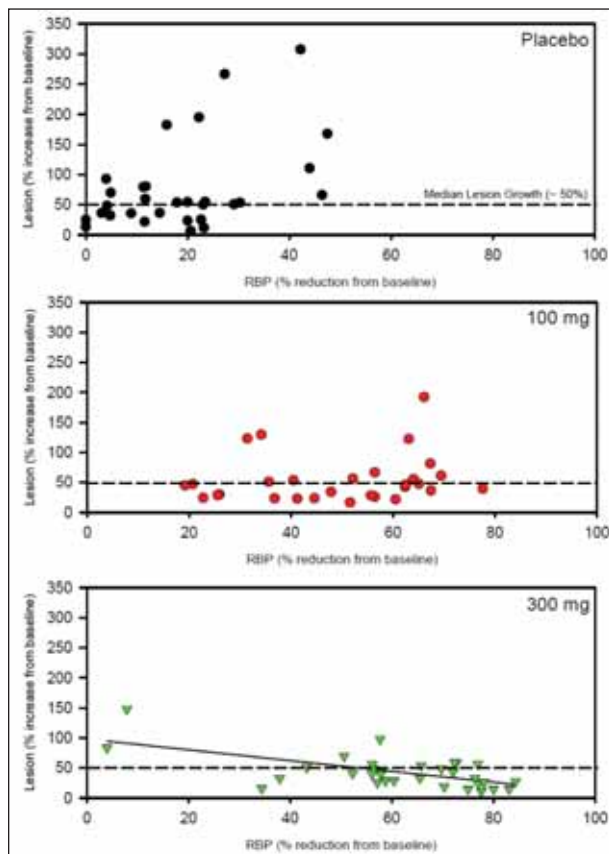


Figure 1. Changes in lesion growth.

exhibited approximately a 40% reduction in the progression of GA compared with the placebo group.

Regarding safety, as anticipated, there was a reduction in dark adaptation in approximately 10% of patients who received fenretinide, compared with those who received placebo. There was also mild elevation of liver function in some patients. Interestingly, dry eye was less severe in the treatment groups than in the control group. It was postulated that this might be due to the elderly nature of the study population.

DISCUSSION

The investigators sought to determine whether the reduction in progression of GA in fenretinide-treated patients in this study was related to a reduction in serum RBP, as hypothesized. Therefore, changes in lesion growth at 24 months were plotted as a function of reduction of RBP (Figure 1). In the 300 mg group, a linear relationship was seen between reduction in serum RBP and the reduced progression of GA.

In this interim analysis, the investigators also noted a reduction in the development of exudative AMD in fenretinide-treated patients. More new exudative AMD was

seen in the placebo group (approximately 20%) than in the two treatment groups (approximately 10%). This response was not dose-dependent.

This finding suggested that there might be an antiangiogenic mechanism at work, in addition to fenretinide's effect on RBP, so experimental work was performed to investigate this further. In a human RPE cell culture model, vascular endothelial growth factor (VEGF) expression in response to oxidative stress was reduced with fenretinide pretreatment. In a hyperglycemic mouse model, VEGF expression was reduced in animals that received fenretinide for 30 days, compared with control mice.

To evaluate whether this reduction in VEGF expression led to an effect on neovascularization, another animal study was performed. Mice pretreated with fenretinide developed less corneal neovascularization than the control group after being challenged with fibroblast growth factor pellets. Taken together, this work suggests that fenretinide has an effect on VEGF production and a resulting antiangiogenic effect.

CONCLUSIONS

Interim results in this phase 2 study suggest that treatment with fenretinide slows lesion growth in patients with GA, the primary endpoint of the study. Fenretinide-mediated reductions in RBP correlated with reduced GA growth, suggesting that RBP reduction is the drug's mechanism of action. Fenretinide also showed a trend for reducing the rate of conversion from dry to wet AMD. This reduction was not dose-dependent, suggesting a second mechanism of action, which was confirmed in animal studies. Fenretinide treatment was generally well tolerated, with anticipated side effects.

The apparent efficacy of fenretinide against both wet and dry forms of AMD, if confirmed in further studies, would be unique, making fenretinide a promising agent for treatment of early stages of AMD.

Final results of the study discussed here are expected to be presented later this year. ■

Alexander M. Eaton, MD, is the Founder and Director of the Retina Health Center in Fort Myers and Naples, FL. Dr. Eaton states that he has no direct financial interest in the outcomes of the study discussed in this article. He may be reached at +1 239 337 3337 or +1 239 793 5200.



1. Sparrow JR, Kim SR, Wu Y. Experimental approaches to the study of A2E, a bisretinoid lipofuscin chromophore of retinal pigment epithelium. *Methods Mol Biol.* 2010;652:315-327.
2. Radu RA, Han, Y, Bui T, et al. Reductions in serum vitamin A arrest accumulation of toxic retinal fluorophores: a potential therapy for treatment of lipofuscin-based retinal diseases. *Invest Ophthalmol Vis Sci.* 2005;46:4393-4401.
3. Eaton AM, Slakter JS, McLead K, et al. Pilot study of the efficacy and safety of fenretinide 100mg and 300mg compared to placebo in subjects with geographic atrophy (GA). Paper presented at: American Society of Retina Specialists annual meeting; Vancouver, Canada.