Integrin Peptide Therapy in Choroidal and Retinal Neovascularization

This novel approach to vascular eye disease has several indications.

BY HUGO QUIROZ-MERCADO, MD

Traditional therapy for vascular eye disease is making way for an emerging class of treatment. Scientists are proposing a novel approach for choroidal and retinal neovascularization with an unconventional mechanism of action—targeting integrins instead of vascular endothelial growth factor (VEGF). Integrins play a key role in cell signaling and regulating cellular shape, motility, and the cell cycle. Ophthalmic intravitreal injections of the synthetic anti-integrin oligopeptide ALG-1001 (Allegro Ophthalmics, LLC) not only inhibit the production of VEGF but also turn off, reduce leakage of, and inhibit the growth of aberrant blood vessels. ALG-1001 prevents cell adhesion mediated by αvβ3, αvβ5, and α5β1 integrins, which are all sites that are expressed in neovascular ocular tissue in wet age-related macular degeneration (AMD) and diabetic retinopathy. The new approach has the potential to be an effective standalone treatment as well as a complement to the existing standard of care.

Traditional anti-VEGF treatment for vascular eye diseases inhibits VEGF that has already been produced. Integrin peptide therapy differs in that it forces endothelial cells to stop the production of VEGF and the entire neovascular construction process. ALG-1001 binds several receptors in the cells and inhibits multiple pathways in this process.

CLINICAL FINDINGS

ALG-1001 is currently being investigated for 3 indications: wet AMD, diabetic macular edema (DME), and vitreomacular traction (VMT). The Wet AMD Study is a dose-ranging, monotherapy study with a primary endpoint of safety and a secondary endpoint of improvement in both best corrected visual acuity (BCVA) and central macular thickness (CMT). The phase 1b/2a, 6-month study was the first clinical trial of ALG-1001 in wet AMD and the first clinical trial evaluating its dose-ranging safety in humans. Fifteen participants received 3 monthly injections of ALG-1001 monotherapy. Patients who received a 3.2-mg dose had a mean BCVA improvement of more than 5 letters 60 days off-treatment, with the benefit maintained 120 days off-treatment (Figure 1). Additionally, BCVA improvement corresponded with a 30% decrease in CMT and improvement in macular architecture.

In a phase 1 study in patients with DME, nearly 55% of participants improved...
the equivalent of 11 letters in BCVA, with at least a 30% reduction in CMT with ALG-1001 monotherapy (Figure 2). A second dose-ranging DME study will observe the additional clinical benefits of integrin peptide therapy in combination with bevacizumab (Avastin, Genentech) vs bevacizumab alone. After 4 monthly injections of either bevacizumab plus sham as a control or bevacizumab plus ALG-1001, participants will be observed for additional improvements in BCVA and macular anatomy over anti-VEGF treatment alone.

I have personally evaluated numerous wet AMD and DME patients treated with ALG-1001. Many of these patients were previously treated with bevacizumab (Avastin, Genentech), and either they failed to respond or their improvement had plateaued. I was impressed to see that after 2 to 3 treatments of ALG-1001, patients often demonstrated further substantial improvements in retinal anatomy and BCVA. What is more promising, these clinical benefits were usually long-lasting, frequently delaying the need for additional treatment for 3 months or longer.

The clinical strategy for ALG-1001 is supported by preclinical research conducted by Peter Campochiaro, MD, at Wilmer Eye Institute at Johns Hopkins University. Dr. Campochiaro conducted a transgenic choroidal neovascularization mouse study, which showed comparable rates of efficacy in regressing choroidal neovascularization in wet AMD between ALG-1001 and ranibizumab (Lucentis, Genentech) monotherapy. However, combined therapy with ALG-1001 and ranibizumab performed 35% better than standalone treatment of either drug. With the same mouse model, Dr. Campochiaro showed that ALG-1001 reduced vascular leakage with statistical significance.

**FUTURE CLINICAL TRIALS**

Now that it has been observed that integrin peptide therapy is safe and well tolerated, attention is being turned to determining the best dosage and dosing regimen. Doses of 3.2 mg and 2.0 mg have been analyzed, but it is not yet known which dose will be best for future studies. The small study sample of wet AMD patients who received 3.2 mg have had considerable improvements in BCVA and decreased CMT, and the same is true for the small study sample of DME patients who received 2.0 mg. The increased 3.2 mg dosage may reduce the number of injections that patients need. Combining that dosage with angiogenic therapies may have a better clinical effect in our patients, so the next step will also be determining the best combination with other angiogenic therapies.

Despite the progress made with anti-VEGF therapy, vascular eye disease has been quite challenging to treat. Therapy can be burdensome and, over time, can decline in efficacy or simply not provide enough effect to prevent progression of the disease. While additional work needs to be done to understand this unique new drug class that targets integrins, the early results make me very optimistic that we will soon have additional treatment options to offer our patients.

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