Integrin Peptide Therapy for the Treatment of Vascular Eye Diseases

In addition to its effects in DME, this molecule can induce posterior vitreous detachment.

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A new small molecule, a synthetic oligopeptide that holds promise as a novel modality for treating neovascular diseases of the eye, has also demonstrated the ability to induce posterior vitreous detachment (PVD) in early clinical investigation.

This peptide, dubbed ALG-1001 (Allegro Ophthalmics, LLC), operates via a number of mechanisms that may make it a valuable addition to our therapeutic arsenal, if the positive results seen to date in early clinical trials are sustained in future investigations. ALG-1001 works via a pathway distinctly different from VEGF inhibition, targeting different aspects of the angiogenic cascade. In addition to the potential for use as a standalone therapy for retinal vascular diseases, therefore, it offers the possibility of synergistic or at least additive efficacy when used in combination with anti-VEGF treatment.

Potential therapeutic targets include not only vascular conditions such as choroidal neovascularization (CNV) in age-related macular degeneration and diabetic macular edema (DME), but also vitreous liquefaction and the induction of PVD. An initial proof-of-concept clinical study in patients with DME showed that the effect of the compound lasted at least 3 months after treatment ceased.1 Induction of PVD was also seen in patients in the same phase 1 study. Animal and human studies have to date indicated no safety signals.

INTRODUCING INTEGRIN PEPTIDE THERAPY

The ALG-1001 peptide affects a large class of proteins called integrins, cell surface receptors that perform a number of functions, including cell signal transduction, mediation of attachments between cells, and regulation of the cell cycle. Integrins interact with important proteins such as collagen and fibronectin in the extracellular matrix, and intracellularly they mediate cell survival and trafficking.

By interacting with specific ligands, the peptide interferes with the angiogenic cascade at multiple points and inhibits cell adhesion. It mediates integrin subunits implicated in the angiogenic cascade (α5β1, αvβ3, αvβ5), as well as integrin subunits implicated in PVD and vitreous liquefaction (α3β1).

Peter Campochiaro, MD, and colleagues at the Wilmer Eye Institute of Johns Hopkins University have performed multiple animal safety studies. In a laser-induced
CNV mouse model, the area of laser-induced CNV was reduced by 43%. In a mouse model of preretinal neovascularization (NV), intravitreal injection of 3 doses of the compound resulted in up to 54% inhibition of NV. In a transgenic mouse model expressing human VEGF, a 24% reduction of vascular permeability compared with vehicle \( (P = .017) \) was shown. In that same transgenic mouse model, ALG-1001 and ranibizumab (Lucentis, Genentech) performed equally in inhibiting the area of CNV, and a combination of the 2 agents inhibited the area of CNV 35% better than standalone therapy \( (P = .0385) \). Additionally, in a separate animal safety study performed by Hugo Quiroz-Mercado, MD, and colleagues, doses 4 times greater than the target dose showed no sign of toxicity.

**CLINICAL STUDY**

Study of ALG-1001 in humans has included 15 subjects with advanced DME in a phase 1 trial to assess safety and potential efficacy. These patients had BCVA of 20/100 or worse, some had early proliferative diabetic retinopathy, and many were refractory to standard of care. After a washout period of 90 days with no anti-VEGF, steroid, or laser treatment, patients received 3 intravitreal 2.5-mg injections at monthly intervals as standalone therapy. Follow-up continued for 3 months after the last treatment.

In these 15 patients, mean age at enrollment was 62.5 years, baseline BCVA was 1.0 logMAR (20/200 Snellen equivalent), and baseline central macular thickness (CMT) on optical coherence tomography (OCT) was 519 µm. Four patients had received previous anti-VEGF therapy, and 6 had received previous laser.

No subjects in the study showed loss of BCVA or increase in CMT on OCT. No serious adverse events (AEs) or significant AEs were seen during follow-up. The AEs that were observed were mostly related to the injection and were minor and transient. Among ocular serious AEs and AEs, 1 subject had transient intraocular pressure (IOP) elevation that resolved spontaneously, and 2 had transient mild intraocular inflammation after injection that resolved quickly with topical steroid treatment. Three subjects were lost to follow-up for reasons not related to the study.

In addition to the safety results, preliminary indications of efficacy were seen in these 15 subjects. Mean BCVA in all subjects improved from 1.0 (20/200) at baseline to 0.81 (20/125) at 60 days (last treatment) and was maintained at 0.75 (20/125) at 150 days (final follow-up, 3 months off treatment).

This modest improvement of a mean of about 2
lines of vision (persisting 90 days off treatment) does not tell the whole story, however. Eight patients who demonstrated at least 3 lines of improvement at day 90 were considered responders, and these patients were analyzed separately from a group of 7 nonresponders. The responders improved from a mean 1.08 (20/200) at baseline to 0.7 (20/100) at 60 days and 0.7 (20/100) at 150 days. Nonresponders started at 0.91 (20/160) and remained at 0.94 (20/160) at 60 days, with slight improvement to 0.76 (20/125) at 150 days (Figure 1).

Regarding anatomic outcomes, in all subjects, mean CMT of 519 µm at baseline was reduced to a mean of 387 µm at 150 days. Among responders, mean baseline of 563 µm was reduced to a mean of 307 µm at 150 days, whereas nonresponders started at 468 µm and ended at 481 µm at 150 days (Figure 2). Examples of some individual patients’ responses are shown in Figure 3.

It should be noted that, for patients considered nonresponders, there was no significant loss of BCVA or CMT.

PVD

ALG-1001 has also been evaluated in animals and this same group of human subjects for its ability to induce PVD. ALG-1001 interferes with cell-to-cell and cell-to-extracellular matrix adhesion to cause vitreous liquefaction and PVD. Binding of the compound to the α3β1 receptor leads to the release of cellular adhesion between the vitreous and retina, which induces PVD.

This has been tested in animals, again in work primarily done by Quiroz-Mercado and coworkers. In a mouse model, a single intravitreal injection led to total PVD in 60% of animals and total vitreous liquefaction in 80% of animals at 24 hours, as confirmed by pars plana vitrectomy.

In the human clinical study, subjects’ PVD status was determined at baseline and at monthly intervals thereafter. PVD was assessed at 3 locations—the optic nerve, the macula, and the midperiphery—with kinetic ultrasound B-scan.

Of 11 patients with no or partial PVD at baseline, 6 developed total PVD. Of 5 patients with no PVD at baseline, 3 developed partial PVD. Figure 4 shows a patient with no PVD at baseline and total PVD at day 90.

CONCLUSIONS

Integrin peptide therapy is an emerging class of treatment for vascular eye diseases. The method of action of ALG-1001, the first entity in this class to reach the clinic, is distinctly different from existing therapies, as it targets integrins rather than VEGF. Animal work suggests a possibility that it will have a complementary effect with the existing standard of care.

Preclinical work in animals has shown safety and suggestions of efficacy with ALG-1001 as a standalone therapy and in combination with anti-VEGF therapy.

Clinical evaluation in patients with end-stage DME have shown safety and signs of efficacy with several types of evaluations, including visual acuity and CMT on OCT. Effects of the drug appear to last 3 months after treatment.

This compound also has demonstrated the ability to induce PVD in patients with DME. Significantly, it is notoriously difficult to induce PVD in DME patients with nonproliferative diabetic retinopathy.

Further work is under way; a phase 1/2 study in patients with wet age-related macular degeneration has begun, and early results are promising.

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Figure 4. Patient with (A) no PVD at baseline and (B) total PVD at day 90.