ANTI-INTEGRIN THERAPY IN TREATMENT OF DME

Agent shows novel mechanism of action, binding in the retina to stop angiogenesis.

BY PETER K. KAISER, MD

Integrins have recently emerged as a treatment target in vitreoretinal diseases. Like VEGF, they are a part of the angiogenic cascade. Integrins are involved in cell-surface interactions that allow new endothelial cells to grow in the extracellular space. Without the expression of integrins, neovascularization would not occur. Integrin receptors cross-activate receptors for VEGF and for platelet-derived growth factor, demonstrating that these factors are closely interrelated in the angiogenesis pathway.

Integrins are a molecular family involved in angiogenesis; each consists of noncovalently bound alpha (α) and beta (β) subunits. Endothelial cells express many different integrins, but certain ones are more important in angiogenesis. Integrin $\alpha v\beta 3$ has been observed in choroidal neovascularization associated with wet age-related macular degeneration (AMD), and integrins $\alpha v\beta 3$ and $\alpha v\beta 5$ have been observed in neovascularization associated with proliferative diabetic retinopathy (DR).[1] Other research shows that integrin $\alpha 5\beta 1$ is expressed in neovascular ocular tissue in patients with wet AMD and DR.[2] Targeting and inhibiting these integrins inhibits VEGF production, endothelial cell proliferation, and vascular construction and reduces leukocyte-mediated inflammation.

MECHANISM OF ACTION

Although researchers have long understood the importance of integrin receptors, previous attempts to use them as a target of therapy relied on large-molecular-weight agents that acted on only one integrin receptor and had to be continually administered intravenously.

ALG-1001 (Luminate, Allegro Ophthalmics) is a synthetic arginine-glycine-aspartic acid class oligopeptide that binds to multiple integrin-receptor sites and affects many pathways of angiogenesis and inflammation. Researchers at the California Institute of Technology, led by Julia A. Kornfield, PhD, and at Johns Hopkins University, led by Peter A. Campochiaro, MD, recently found that, unlike VEGF inhibitors, which bind to VEGF receptors in the vitreous, ALG-1001 binds in the retinal pigment epithelium, where it turns off production of VEGF and interferes with vessel growth.[3] This means that the agent works at the source to shut down the production of VEGF and stop endothelial proliferation. [Editor's Note: Drs. Kornfield, Campochiaro, and Kaiser are on the Scientific Advisory Board of Allegro Ophthalmics.]

ALG-1001 also has been found to have antiinflammatory properties, reducing leukocyte attachment and transendothelial migration through the downregulation of integrin $\alpha M\beta 2$.[3] And ALG-1001 appears to activate a repair mechanism in the retina by increasing neuroprotective genetic activity. This multifaceted mechanism of action seems to help reset the retina to homeostasis.

ALG-1001 also appears to act only on stressed cells. This may explain the drug's excellent safety profile in clinical experience to date, with no drug-related serious adverse events reported in roughly 400 patients treated.

CLINICAL EXPERIENCE

ALG-1001 has been evaluated in a phase 1 clinical safety trial, and topline 6-month results of the phase 2b DEL MAR clinical trial in patients with diabetic macular edema (DME) were recently announced.[3,4] Stage 1 of the controlled,

AT A GLANCE

- Integrins, a part of the angiogenic cascade, have emerged as a treatment target for patients with vitreoretinal diseases.
- Unlike VEGF inhibitors, which bind to VEGF in the vitreous, ALG-1001, an integrin peptide antagonist, binds directly in the target retinal pigment endothelium and turns off the production of VEGF.
- ALG-1001 has also been found to have antiinflammatory properties, reducing leukocyte attachment and transendothelial migration.

Figures courtesy of Allegro Ophthalmics.

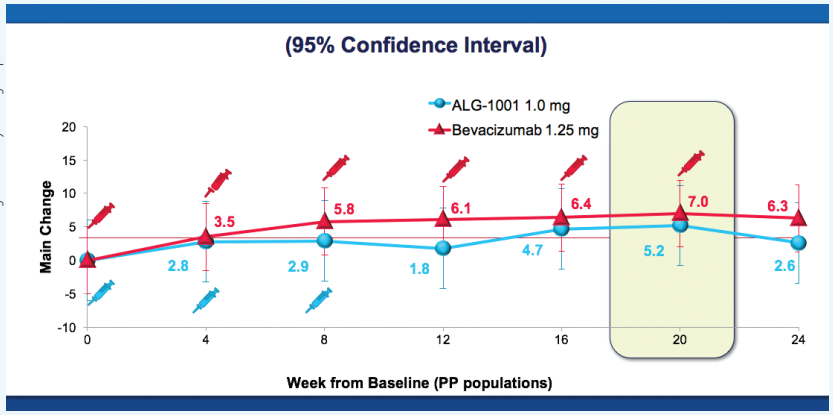

Figure 1. The phase 2b DEL MAR primary endpoint was change in BCVA letters read over time.

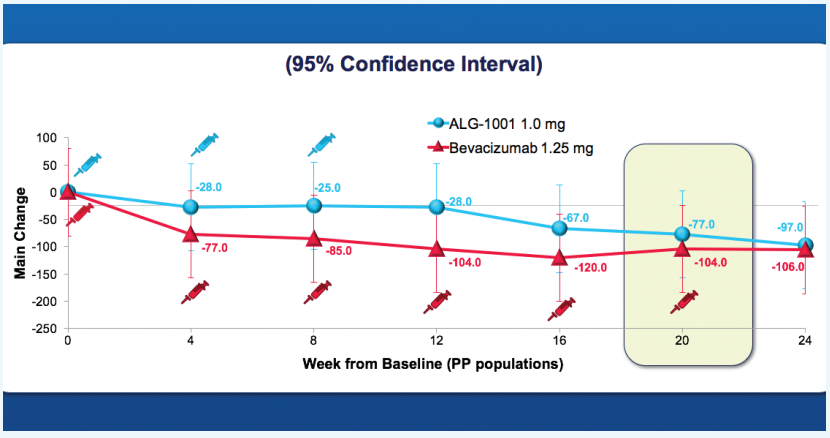

Figure 2. The study's secondary endpoint was the change in central retinal thickness over time.

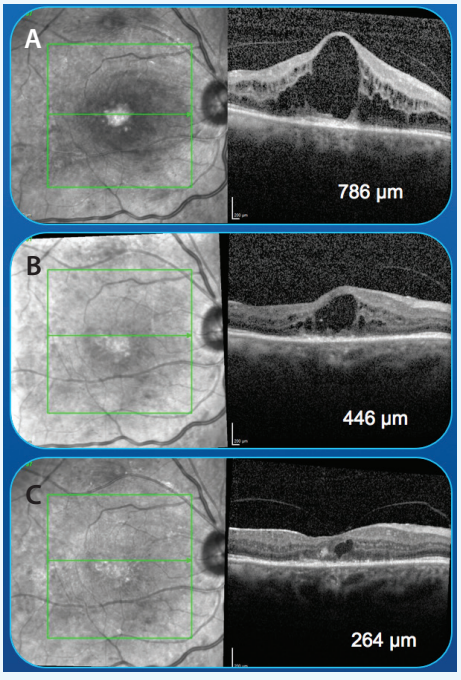

Figure 3. OCT images from one patient in the DEL MAR study showing baseline (A) and results of treatment with ALG-1001 1 mg at week 16, 8 weeks after loading was complete (B), and at week 20, 12 weeks after loading (C).

double masked, dose-ranging DEL MAR study included 136 patients with DME enrolled across 32 US sites. The primary endpoint in this stage of the study was noninferiority to bevacizumab (Avastin, Genentech), defined as 3-letter or less difference in mean best corrected visual acuity (BCVA) at 20 weeks. In three ALG-1001 arms, patients were treated with three monthly loading injections of 1, 2, or 3 mg of the drug followed by 12 weeks off treatment. Patients assigned to the bevacizumab arm received 1.25 mg of the anti-VEGF agent in six monthly injections. Both drugs were used as monotherapy.

The primary endpoint was met, with 7.0 (bevacizumab) versus 5.2 (ALG-1001) letters gained at 20 weeks (Figure 1). The secondary endpoint was also met, with similar reduction in mean optical coherence tomography (OCT) central macular thickness (CMT): -104 µm (bevacizumab) versus -77 µm (ALG-1001) at study week 20 and 106 µm (bevacizumab) versus -97 µm (ALG-1001) at study week 24 (Figure 2). Figure 3 shows the results in one of the study patients.

DISCUSSION

A plot of the distribution of the BCVA and OCT CMT changes from baseline for all four study groups showed a U-shaped dose response curve for ALG-1001, indicating that the best dose is 1 mg. This finding also confirmed the experience in the phase 1 trial and helps provide context as we design phase 3 trials for the drug.

In terms of study design, bevacizumab was given the best chance of success, in that it was administered with a fixed monthly regimen. For ALG-1001, we chose a dosing schedule that allowed us to learn more about the drug. By administering the loading dose of three injections and then following patients over time, we could see what happened to patients in the months after treatment.

ALG-1001, which binds uniquely in the retina, showed impressive long-acting effects. The last dose was at week 8, and primary outcome was evaluated at week 20. Patients' visual acuity increased from the end of treatment at week 8 to week 20, which was perhaps a bit of a surprise in these diabetic individuals. The bevacizumab group had gained 7 letters at week 20.

It is important to note that integrin antagonist treatment takes longer than anti-VEGF therapy to achieve its effect. ALG-1001 acts earlier in the pathway to stop VEGF production. It does not affect the clearance of VEGF that existed prior to treatment.

NEXT STEPS

Stage 2 of the DEL MAR phase 2b trial is under way. This stage of the trial is evaluating vision and durability with ALG-1001 as combination or adjunctive therapy for DME. Investigators will follow 75 patients for 5 months; in one arm, patients receive monthly injections of ALG-1001 plus bevacizumab for 3 months, and in the other arm patients will receive an initial injection of bevacizumab followed by monthly monotherapy with ALG-1001. Top line results of stage 2 are anticipated in the third quarter of this year.

A PROMISING ALTERNATIVE OR ADJUNCT

In clinical trials to date, ALG-1001 has shown robust activity in DME. This first-in-class integrin inhibitor is directly antiinflammatory and essentially turns off the machinery of angiogenesis. Stage 1 data from the DEL MAR phase 2 study confirmed the durability seen in phase 1 with 12 weeks of ALG-1001 monotherapy. Although the agent is similar in potency to anti-VEGF therapy, it has a completely different mechanism of action.

ALG-1001 is one of the few agents in late-stage development that has been shown to be successful as monotherapy, with half the number of injections, when compared head-to-head with anti-VEGF therapy. ■

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