

Integrin Peptide Therapy

A new class of treatment for patients with vascular eye disease.

REVIEWED BY DAVID BOYER, MD

Integrin peptide therapy is a new approach to treating neovascular eye diseases. A small molecule, ALG-1001, interferes with several pathways of the angiogenic cascade by binding to multiple integrin-receptor sites known to be implicated in both choroidal and preretinal neovascularization.

Integrins have long been associated with choroidal neovascularization (CNV), wet age-related macular degeneration (AMD), and diabetic retinopathy, but there are different integrins that are involved in different forms of neovascularization. Previous attempts to inhibit integrins have failed because none of the past treatments targeted all integrin receptors. Rather, antibodies were working on 1 receptor. Additionally, the antibodies required frequent administration due to the short half-life. ALG-1001 binds to all integrin receptors involved with retinal angiogenesis and has a long-lasting effect.

CLINICAL TRIAL DATA

Based on human and animal studies to date, integrin peptide therapy has been effective in treating diabetic macular edema (DME) and wet AMD with treatment benefits lasting at least 3 months. A phase 1 proof-of-concept study on DME has been completed, and a phase 1b/2a study on wet AMD is currently in progress.¹

The phase 1 proof-of-concept study on DME showed the drug was safe and gave encouraging efficacy data. Fifteen end-stage DME patients—many of whom were refractory to the current standard of care—received 3 monthly loading doses and then were followed for 3 months off of treatment. There was a 90-day washout period from any anti-VEGF, laser, or steroid treatment, and there were no serious or significant adverse events.

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Improvements in anatomy were exhibited in 8 of 15 subjects who experienced a reduction in their central macular thickness by optical coherence tomography (OCT) ranging from 30-80%. This reduction held until the end of the study, which was 3 months after treatment was completed. Improvement in best corrected visual acuity (BCVA) was exhibited in 8 out of 15 subjects who had an improvement in BCVA of 3-5 lines with 4 patients going from legally blind to functional vision. Like the reduction in OCT central macular thickness, the improvement held 3 months after treatment ended. The results are fairly substantial, as more than half of the patients had improved BCVA.

The subjects in the phase 1b/2a study are wet AMD patients, as opposed to DME patients in the first study, but the design is very similar. This study is a 30-patient, dose-ranging, safety and efficacy study. Patients are being followed 4 months off of treatment instead of 3 months. The study is currently enrolling subjects, and early data are encouraging.

THERAPEUTIC OPTIONS

It is possible that ALG-1001 can be administered as either a standalone therapy or in combination

with anti-VEGF therapy. This is based upon both human and animal clinical trial data. Peter Campochiaro, MD, of Wilmer Eye Institute has performed numerous animal studies with ALG-1001. In a standalone study using a CNV mouse model that mimicked wet AMD, ALG-1001 regressed CNV by more than 40%. In another standalone study using a retinopathy of prematurity mouse model that mimicked DME, ALG-1001 regressed neovascularization by more than 50%. In a transgenic mouse model that expressed human VEGF, Dr. Campochiaro looked at both stand-alone ALG-1001 vs ranibizumab (Lucentis, Genentech) and the combination of the 2 drugs. ALG-1001 standalone treatment and ranibizumab standalone treatment achieved comparable rates of efficacy in regressing CNV. The combination of ALG-1001 and ranibizumab performed 35% better than either drug on its own, with statistical significance. In the phase 1 human proof-of-concept study, only some of the responders were subjects that received prior anti-VEGF and/or laser treatment.

The ophthalmic industry currently has excellent anti-VEGF therapies that are phenomenal. The bar is set high, so it is very possible to use ALG-1001 in conjunction with other agents to improve results.

INTEGRIN PEPTIDE DIFFERS FROM ANTI-VEGF THERAPY

Integrin peptide therapy is different from anti-VEGF therapy in 3 key ways. First, it inhibits integrin instead of just targeting VEGF. Second, ALG-1001 is a small oligopeptide instead of a large monoclonal antibody. It is 1/1000th the size of a monoclonal antibody. Third, unlike other approaches that target integrin, the shape, size and configuration of ALG-1001 allows it to successfully inhibit multiple integrin receptor sites implicated in angiogenesis (Figure 1). More specifically, integrin peptide therapy inhibits multiple mechanisms that are associated with the neovascularization process, making it take longer for the entire neovascularization process to restart itself. This is evidenced by the initial human efficacy data showing clinical benefit in BCVA and OCT central macular thickness from ALG-1001 3 months off of treatment after an initial loading dose.

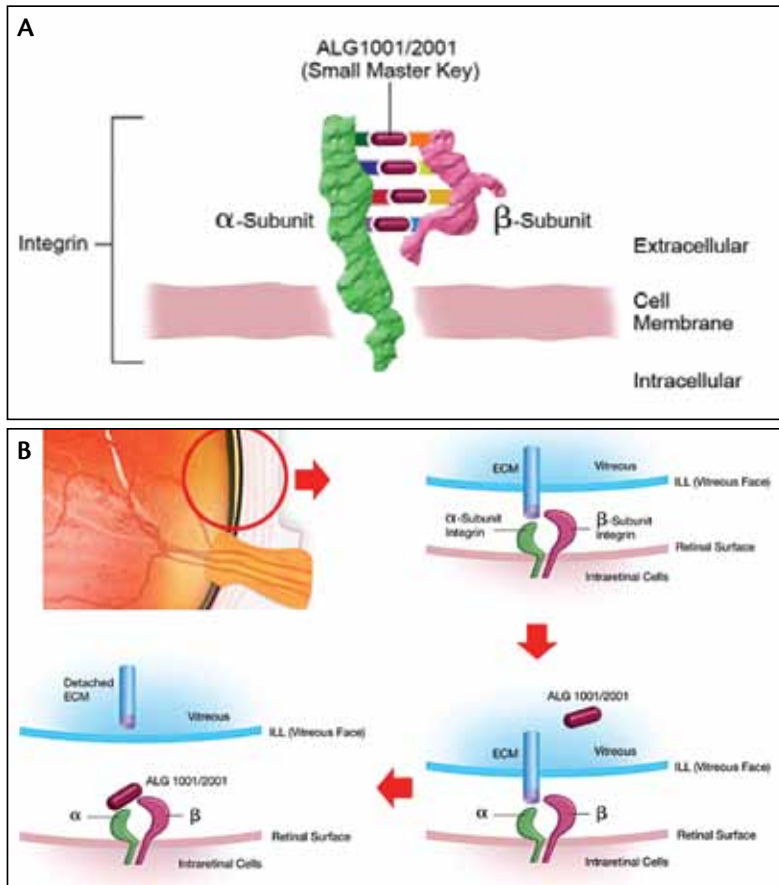


Figure 1. Integrin (A) binds to the integrin receptor sites to block abnormal blood vessels and to interfere with cell-to-cell adhesion (B).

NEXT STEPS

Building upon the results of the phase 1 DME study, a phase 1b/2a wet AMD study is in progress. It is a dose-ranging, 6-month study with 30 subjects being followed 4 months off of treatment. Very early results look promising. This study, combined with the completed phase 1 DME study, will be the basis for a phase 2 wet AMD study in the United States in 2013. The combination of clinical and preclinical data to date provides hope that this new therapy will be a viable option for patients suffering from vascular eye diseases. ■

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1. Boyer D. Diabetic retinopathy - clinical research II. Presented at the Annual Meeting of Association for Research in Vision and Ophthalmology; May 2012; Fort Lauderdale, FL.