Intravitreal VEGF Trap for AMD: An Update

The CLEAR-IT 2 Extension Study was presented at the annual meeting of the Association for Research in Vision and Ophthalmology.

BY JEFFREY S. HEIER, MD

The CLEAR-IT 2 trial was a phase 2 study of the safety and efficacy of VEGF Trap-Eye (Regeneron Pharmaceuticals) in patients with neovascular age-related macular degeneration (AMD). The results of the phase 2 trial were presented at the 2008 Retina Society meeting.[1] An extension of the CLEAR-IT 2 trial followed patients from the original trial; 6-month results of the extension stage of the study were presented at the Association for Research in Vision and Ophthalmology (ARVO) earlier this year.[2] This article reviews results of the initial CLEAR-IT 2 as well as data from the extension stage.

CLEAR-IT 2

VEGF Trap-Eye is a purified formulation of VEGF Trap, a vascular endothelial growth factor (VEGF) receptor

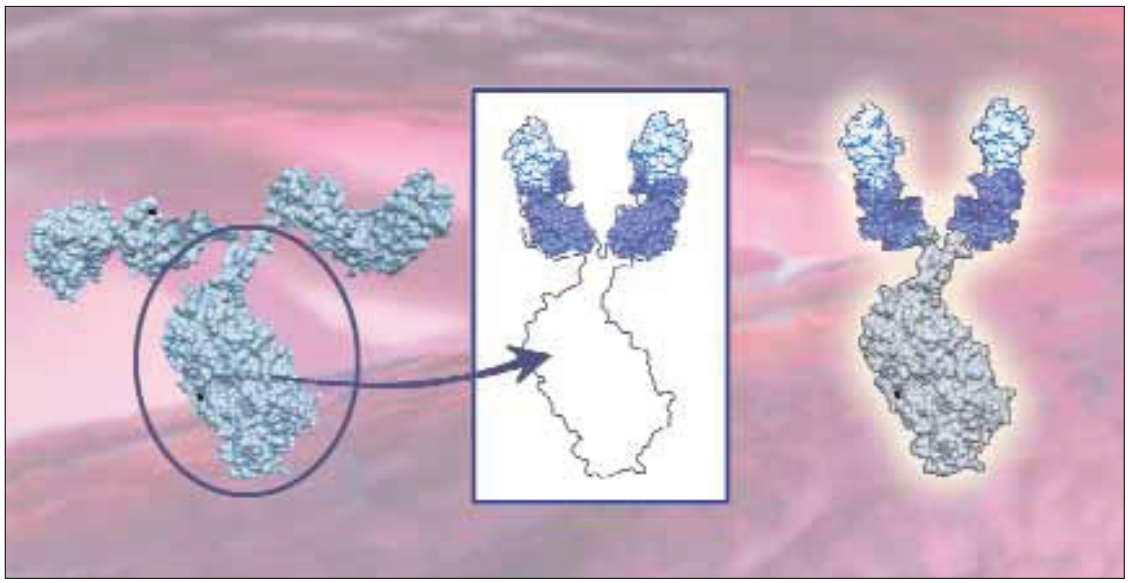

Image courtesy of Jeffrey S. Heier, MD

Figure 1. VEGF Trap-Eye is a fusion protein designed to bind all forms of the proteins VEGF-A and PLGF, which both play a part in abnormal growth of new blood vessels.

fusion protein that binds all forms of VEGF-A (Figure 1). VEGF Trap-Eye, formulated for intraocular use, is being developed for the treatment of neovascular AMD, diabetic macular edema, and other ocular pathologies.

CLEAR-IT 2 was a double-masked multicenter trial in which patients with neovascular AMD were randomly assigned to receive monthly intravitreal injections of VEGF Trap-Eye 0.5 mg or 2.0 mg or quarterly injections of 0.5, 2.0 or 4.0 mg for an initial 3-month fixed-dose period, after which they received the same doses on an as needed basis at monthly visits out to 1 year. Subgroups of patients were established based on age, best-corrected visual acuity (BCVA) at baseline, lesion size at baseline, and previous treatment for neovascular AMD.

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At 1 year, for all treated groups combined (n=157), there was a significant improvement in BCVA from baseline (mean improvement 5.3 letters; *P*<.0001). Patients who received three monthly doses of 2.0 mg followed by as-needed dosing achieved mean improvements in BCVA of 9.0 letters from baseline (*P*<.0001 vs baseline). Those who received three monthly doses of 0.5 mg followed by as-needed dosing achieved mean improvements of 5.4 letters from baseline (*P*<.085 vs baseline) at the end of 1 year. Patients who received initial quarterly dosing followed by as-needed dosing also achieved gains in BCVA, but they were generally not as robust as those achieved with initial monthly dosing.

Patients receiving initial monthly doses of VEGF Trap-Eye achieved mean decreases in retinal thickness vs baseline at 1 year. In addition, treatment with VEGF Trap-Eye was associated with a reduction in the size of the total active choroidal neovascular membrane (CNV).

Subgroup analyses were presented at this year's ARVO meeting. Patients 75 years old or less achieved greater BCVA gains than those older than 75 years. Other differences between subgroups did not achieve statistical significance.

EXTENSION STUDY

Six-month results for 117 patients who elected to enter the extension stage of the CLEAR-IT 2 study were also presented at this year's ARVO. All patients received 2.0 mg VEGF Trap-Eye on an as-needed basis.

In the original study, the mean gain in BCVA from baseline for the 117 patients who entered the extension stage was 7.3 letters (*P*<.0001 vs baseline) at the 3-month primary endpoint of the original study, 8.4 letters (*P*<.0001 vs baseline) at 1 year, and 7.1 letters (*P*<.0001 vs baseline) at month 6 of the extension study. Over the 15-month course of the PRN dosing phase, from month 3 of the original study to month 6 of the extension phase, patients received a mean 3.5 injections of VEGF Trap-Eye.

The treatment was generally well tolerated throughout the study, and there were no drug-related serious adverse events. One case of culture-negative endophthalmitis/uveitis was reported in a study eye, and there were two arterial thrombotic events that were deemed not to be related to the drug. Three deaths were reported, two related to cancers and one in a patient with pre-existing pulmonary hypertension. The most common adverse events were those typically associated with intravitreal injections, including conjunctival hemorrhage at the injection site and transient increased intraocular pressure following injection.

CONCLUSION

The extension study demonstrates that patients with neovascular AMD achieved and maintained significant improvement in BCVA for 18 months with initial fixed dosing followed by 15 months of as-needed administration. On average, only 3.5 injections were given during the PRN dosing phase. Patients continue to be seen and treated in the extension stage of the CLEAR-IT 2 study. ■

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1. Brown D. One year results of a phase 2, randomized, controlled dose- and interval-ranging study of intravitreal VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Paper presented at: Retina Society annual meeting; September 25-28, 2008; Scottsdale, AZ.
2. Heier JS, CLEAR-IT 2 Investigators. CLEAR-IT 2: Phase 2, randomized, controlled dose-and interval-ranging study of intravitreal VEGF Trap Eye in patients with neovascular age-related macular degeneration: predictive factors for visual acuity outcome at one year. Paper presented at: Association for Research in Vision and Ophthalmology annual meeting; May 4, 2009; Fort Lauderdale, FL.

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