

VEGF Trap for the Treatment of Neovascular AMD

VIEW 1 and VIEW II phase 3 studies showed the molecule to be noninferior to ranibizumab.

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Current anti-vascular endothelial growth factor (anti-VEGF) therapy has dramatically altered the ability to treat choroidal neovascularization (CNV) in age-related macular degeneration (AMD). When the strict regimens of the phase 3 trials with ranibizumab (Lucentis, Genentech), MARINA and ANCHOR, are followed, the large majority of patients achieve stability and significant visual gain is seen in upwards of 30% to 40% patients. Unfortunately, in many if not most cases, these outstanding outcomes are dependent upon frequent injections or at least at a minimum, frequent follow-up. When clinicians deviate from that pattern, the outcomes are often less robust. As was seen in MARINA and ANCHOR, patients achieved outstanding gains in the initial treatments and continued maintenance with monthly injections to 2 years.^{1,2}

When looking at varying treatment regimens, such as in PIER and SAILOR, however, the initial gains in visual acuity are often lost when deviating from frequent injections of ranibizumab.^{3,4}

This, however, is not a new concept. In the VISION study for pegaptanib sodium (Macugen, Eyetech) for wet AMD, patients who were randomized after 1 year of therapy maintained their level of vision to 2 years, as opposed to the drop off in vision seen in patients who did not receive maintenance therapy.⁵

Can variable dosing lead to significant visual gain? Rosenfeld et al demonstrated in the PrONTO study this to be true,⁶ but it must be noted that the patients in this study were followed extremely closely and retreated based on strict retreatment criteria. The combination of

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these trial results indicates that although we can clearly achieve robust outcomes with current anti-VEGF therapy, patients require frequent injections and/or at a minimum, frequent follow-up.

The worry of retina specialists is not so much a small loss of vision in terms of two or three letters; rather, the fear is that of a catastrophic event, such as a submacular hemorrhage that can occur no matter how closely followed these patients are. Levine et al⁷ published a retrospective report of six patients who had been treated and stabilized with antivasculature endothelial growth factor (anti-VEGF) agents. Three of the eyes experienced macular hemorrhage within 4 weeks of having a stable examination. Further, one of the eyes was shown to be completely dry on optical coherence tomography (OCT) 1 day prior to the macular hemorrhage, demonstrating that even in the environment of frequent anti-VEGF injections and close follow-up, patients can fail therapy with such regimens. It is in this environment that data from the clinical trials for VEGF trap (VEGF Trap-Eye, Regeneron Pharmaceuticals, Inc.) are reviewed. Data from VIEW 1⁸ were presented by Jeffrey S. Heier, MD; and data from VIEW 2⁹ were presented by Ursula Schmidt-Erfurth, MD, at the Angiogenesis,

Exudation, and Degeneration 2011 meeting in Miami on February 12, 2011.

VEGF TRAP: MECHANISM OF ACTION

VEGF trap is a unique molecule—it is a fusion protein that has been designed as a soluble decoy clonal receptor expressed in the domains of VEGF receptor 1 and 2. It's a fusion protein that binds to all forms of VEGF-A and placental growth factor. The binding sites have the highest affinity for each receptor, 40- to 50-fold higher than current anti-VEGF therapies are fused to dual binding arms, which are attached to an Fc fragment to provide molecular consistency (data on file, Regeneron). The role of the Fc fragment is to prolong the half-life of aflibercept action via a recycling mechanism.

When Stewart et al¹⁰ calculated biological activity of aflibercept 0.5 mg, 2 mg, and 4 mg relative to ranibizumab at 30 days, they found an equivalent intravitreal VEGF-binding activity for the 0.5 mg dose at 73 days, the 2 mg dose at 83 days, and the 4 mg dose at 87 days. The modeling used to make these calculations was based upon the binding affinities and proposed half-lives of each agent.

VIEW 1 AND VIEW 2: DESIGN AND METHODS

VIEW 1 and VIEW 2 were parallel trials performed in the North America and Europe, Asia, and Latin America, respectively. Both were randomized multicenter active-controlled double-masked trials. Patients were randomized evenly to one of four treatment groups: 0.5 mg ranibizumab monthly, VEGF trap 0.5 mg monthly, VEGF trap 2 mg monthly, or VEGF trap 2 mg dosed every 8 weeks following a three-injection loading dose.

VIEW 1 enrolled 1,217 patients and VIEW 2 enrolled 1,240 patients, with a total of 2,457 patients with active treatment-naïve neovascular AMD being evaluated, making this the largest clinical trial performed in retina.

Baseline demographics of VIEW 1 and VIEW 2 were well matched within the two individual studies, although there were more Asian patients in VIEW 2 (20% of study group), and patients were slightly younger. Baseline vision was at approximately 20/100 and the central retinal lesion composition was similar.

VIEW 1 OUTCOMES⁸

Prevention of moderate vision loss was achieved in 94% to 96% in all four groups and all doses and treatment schemes of VEGF trap were found noninferior to ranibizumab. The 0.5 mg monthly group achieved a mean gain of seven letters, the 2 mg monthly group a mean just under 11 letters, and the 2 mg dosed every 8 weeks after the initial loading dose gained a mean just

under eight letters. The ranibizumab monthly group, in comparison, gained a mean eight letters of visual acuity. The only statistically significant difference was found between the monthly ranibizumab and the monthly 2 mg dose of VEGF trap (with the VEGF Trap 2.0 mg dose demonstrating superiority).

There were very few serious ocular adverse events in any of the four groups and the numbers of serious systemic adverse events was also relatively low. Death occurred in 1.6% of the ranibizumab group and in 1.3% for all the VEGF trap groups combined. Vascular events occurred in 1.6% of the ranibizumab and all of the VEGF trap groups.

VIEW 2 OUTCOMES⁹

As with the VIEW 1 study, the primary endpoint of prevention of moderate visual acuity loss was achieved in all the groups in VIEW 2. Ninety-four percent to 96% of patients maintained visual acuity in the range of +3 or -3 lines, indicating that VEGF trap at all doses was noninferior to ranibizumab.

As with VIEW 1, the ocular, systemic, and vascular adverse events were infrequent.

CONCLUSIONS

VEGF trap was well tolerated across all doses and dose regimens and demonstrated similar ocular and systemic safety profiles as ranibizumab. Furthermore, the visual acuity and anatomical outcomes in VIEW 1 and VIEW 2 suggest that VEGF trap has the potential to deliver the same outstanding visual and anatomic outcomes with less frequent dosing to achieve a significant decrease in the treatment burden that patients, their families, and clinicians have come to incur. ■

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