

Aflibercept (VEGF Trap-eye): the newest anti-VEGF drug

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The introduction of anti-vascular endothelial growth factor (anti-VEGF) drugs to ophthalmology over the past 7 years has revolutionised the treatment of exudative age-related macular degeneration (AMD) and holds great promise for diabetic macular oedema, branch and central retinal vein occlusions, and retinopathy of prematurity. Each of the three available drugs (pegaptanib, bevacizumab and ranibizumab) was eagerly embraced by surgeons, but the subsequent clinical results have been mixed, and the regulatory hurdles, particularly those regarding off-label use of bevacizumab, have been challenging.

Into this mix enters aflibercept (VEGF Trap-eye (VTE); Eylea, Regeneron, Tarrytown, New York, USA), for which the US Food and Drug Administration granted approval for the treatment of subfoveal choroidal neovascularisation due to AMD on 18 November 2011. In contrast to the antibody-based VEGF binding strategy used by ranibizumab and bevacizumab, the VTE incorporates the second binding domain of the VEGFR-1 receptor and the third domain of the VEGFR-2 receptor.¹ By fusing these extracellular protein sequences to the Fc segment of a human IgG backbone, in a manner similar to the rheumatoid arthritis drug etanercept, developers have created a chimeric protein with a very high VEGF binding affinity ($K_d \approx 1$ pM).² Like ranibizumab and bevacizumab, the VTE binds all isomers of the VEGF-A family, and although the clinical significance of this is not yet known, it also binds VEGF-B and placental growth factor.

The approval application draws on the strengths of two concurrent AMD trials: the VIEW 1 trial, which enrolled 1217 patients in North American centres, and the VIEW 2 trial, which enrolled 1240 patients in South American, European, Asian and Australian centres. Each trial randomised patients among four treatment arms: monthly 0.5 mg VTE,

monthly or bimonthly 2 mg VTE, and monthly 0.5 mg ranibizumab. All VTE investigational arms reached the primary endpoint—non-inferiority for maintenance of vision (≤ 15 letters of vision loss) compared to ranibizumab (94% for ranibizumab arms and 95% to 96% for all VTE arms).³

Physicians will naturally question what advantage, if any, the VTE brings to our treatment of chorioretinal vascular diseases. Though many factors determine drug selection, most retina surgeons will ask three important questions. What is the peak effect of the drug (usually measured by letters of improvement)? What is the duration of action (usually determined by the frequency of drug administration)? Is the drug safe (usually determined by systemic adverse events)?

Since pegaptanib use is infrequent, the VTE enters a clinical environment dominated by the two closely related antibody-based drugs, bevacizumab and ranibizumab. The clinical superiority of ranibizumab over both observation and photodynamic therapy was well documented in both the MARINA⁴ (7.2 letters vs -10.4 letters) and ANCHOR⁵ (11.3 letters vs -9.5 letters) studies, thus establishing ranibizumab as the standard against which all subsequent drugs are compared. Due in part to its off-label use in ophthalmology, bevacizumab has never been subjected to comparable controlled trials, but the recently reported Comparison of Age-related Macular Degeneration Treatment Trials demonstrated its near equivalency to ranibizumab with monthly dosing (8.0 letters vs 8.5 letters) and non-significantly poorer outcomes with as needed dosing (5.9 letters vs 6.8 letters).⁶ Most physicians, therefore, now believe the two drugs to be clinically equivalent.

Several lines of evidence suggest that the VTE is an effective neutraliser of VEGF. The receptor sequences of the VTE provide powerful VEGF binding (140 times that of ranibizumab) and the molecule's intermediate size 110 kD (compared to 48 kD for ranibizumab and 148 kD for bevacizumab) create a 1 month intravitreal binding activity that exceeds both ranibizumab and bevacizumab.⁷

Treatment of neuroblastoma xenografts in mice, with drugs similar to those used in AMD, showed the following comparative efficacies: VEGF Trap > anti-VEGF monoclonal antibody > aptamer to VEGF₁₆₅.⁸

The most important comparison, however, comes directly from the VIEW trials, where the data for the highest dose of VTE (2 mg monthly) are mixed when compared to ranibizumab. The VIEW 1 trial showed that monthly injections of 2 mg VTE led to greater vision gains than ranibizumab (10.9 letters vs 8.1 letters; $p < 0.05$) whereas no statistically significant difference was seen in the VIEW 2 trial (7.6 letters vs 9.4 letters ($p \geq 0.05$)).³ Since the two trials were comparably sized and followed identical protocols, the reason for this difference in vision improvement is unknown. Since the trials were performed in different parts of the world racial and ethnic differences existed between the two cohorts—predominantly Caucasian patients in VIEW 1 but higher percentages of Hispanic and Asian patients in VIEW 2. The prevalence of choroidal neovascular membrane types differ among races, with idiopathic polypoidal choroidopathy more common in Asian patients. Compared to types 1 and 2 choroidal neovascular membranes, polypoidal choroidopathy does not respond as well to anti-VEGF therapy, thereby leading many physicians to recommend photodynamic therapy for these lesions. However, since inclusion criteria for the VIEW trials were based on the results of fluorescein angiography but not indocyanine green angiography, lesions may have been mischaracterised and inadequately treated. A comparative subanalysis of the data will be required to address this difference. An analysis of pooled data from the two trials showed that the patients receiving 2 mg VTE every 8 weeks achieved comparable improvements in vision, suggesting that VTE and ranibizumab have comparable peak efficacies.

Since the completion of the MARINA and ANCHOR studies, physicians have searched for effective dosing regimens that do not require monthly drug injections or examinations. Efforts to stretch the ranibizumab dosing interval to 3 months (PIER) resulted in forfeiting previous vision gains.⁹ The Comparison of Age-related Macular Degeneration Treatment Trials showed that the letters gained with as needed injections were not statistically inferior to monthly injections (ranibizumab: 6.8 vs 8.5; bevacizumab: 5.9 vs

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8.0) but patients still required monthly evaluations to determine the need for re-injection.

The first indication that the VTE may be dosed less frequently came from the phase II CLEAR-IT 2 study where patients required, on average, only two injections between the 12 week loading period and the 52 week termination visit.¹⁰ The phase III trials showed that injections of the 2 mg VTE every 8 weeks delivered comparable letter gains to monthly ranibizumab (VIEW 1: 7.9 vs 8.1; VIEW 2: 8.9 vs 9.4; $p \geq 0.05$ for both) while, for the first time, demonstrating that patients may not require monthly evaluations. Some initial concerns have been raised over the efficacy of bimonthly VTE because patients in the VIEW 2 exhibited small, diminishing 'sawtooth' variations in macular thickness, though visual acuities did not show similar changes. Since patients from the VIEW studies receive as needed dosing (with treatment-free intervals not exceeding 3 months) after the first year and open label, as needed VTE after year 2, future data will better define the efficacy of less frequent, as needed dosing.

Though most retina surgeons acknowledge that monthly injections of ranibizumab has been considered the 'gold standard' against which all other regimens should be compared, the majority use treat-and-extend or treat-and-observe strategies to minimise both the number of injections and office visits. The VIEW trials used a capped 3 month treat-and-observe strategy in year 2 but did not test treat-and-extend, thereby requiring retina surgeons to investigate this strategy with post-approval trials. Nonetheless, the popularity of this approach among both patients and physicians suggests that the VTE will be used in this manner, with the hope of extending the intervals longer than with either ranibizumab or bevacizumab.

Initial use of the VTE for AMD consisted of intravenous injections,¹¹ similar to the original investigation strategy employed with bevacizumab.¹² Patients receiving the higher dose of VTE (3 mg/kg) experienced more systemic hypertension and proteinuria than those treated with the lower dose (1 mg/kg). To simplify drug administration and minimise systemic adverse events, subsequent VTE trials have used only intravitreal injections. Severe extraocular adverse events (stroke, myocardial infarction) in the VIEW trials occurred with similar

frequencies in patients receiving the VTE (0.7% to 2.6%) and ranibizumab (1.6% to 1.7%). This is not surprising since the short systemic half-life of unbound VTE (1.5 days) suggests that systemic VEGF binding, and possibly the incidence of adverse events, may closer mimic ranibizumab (half-life of 6 h) rather than bevacizumab (half-life of 20 days).

A phase III VTE trial for central retinal vein occlusion has completed enrolment, and similar trials for background diabetic retinopathy and branch retinal vein occlusion have begun. As physicians become more comfortable with use of the VTE, physician initiated trials of other chorioretinal and anterior segment conditions will likely begin.

Although many factors determine physicians' choices of anti-VEGF drugs for the treatment of AMD, the significant difference in cost between ranibizumab and bevacizumab has been an important factor. The single-dose cost of VTE (\$1850) is comparable to ranibizumab (\$1950), but still substantially more than bevacizumab (approximately \$50). Since the single-dose costs and efficacies of the two drugs are comparable, physicians' use of VTE instead of ranibizumab may largely depend upon their perceptions of the drugs' durabilities. If the results of the 2 mg every 8 weeks VTE treatment arms are validated by post-approval experience, then the cost of treating patients with VTE may be approximately half that with ranibizumab. Cost-conscious physicians, however, will also be forced to consider the relative merits of more expensive, less frequent dosing with VTE versus the more frequently dosed, lower cost alternative, off-label bevacizumab.

Market approval of VTE was based primarily upon the VIEW trials but, unfortunately, these data have not yet been subjected to peer review analysis and publication. Therefore, physicians should use caution when making treatment decisions involving VTE as the only available clinical information comes from professional meetings and internet postings.

The VTE comes as a welcome addition to our expanding arsenal against the major causes of vision loss in developed nations. It appears to have a similar safety profile to ranibizumab, and its longer duration of action as shown by the 2 mg bimonthly results, may enable physicians to administer fewer injections, thereby decreasing the growing burden of AMD patients on

their practices, while simultaneously relieving patients of the need for monthly physician visits.

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