Aflibercept in wet age-related macular degeneration: a perspective review

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Abstract: In the treatment of neovascular age-related macular degeneration (AMD), vascular endothelial growth factor (VEGF) has emerged as a key target of therapy. Currently, patients with neovascular AMD are treated with monthly intravitreal injections of anti-VEGF medications. Aflibercept is a novel recombinant fusion protein engineered to bind all isoforms of VEGF-A, VEGF-B, and placental growth factor. It is the latest medication to receive US Federal Drug Administration (FDA) approval for the treatment of neovascular AMD. Theoretical models suggest this molecule may have a longer duration of action compared with current treatments. The results of the VEGF Trap-Eye: Investigation of Efficacy and Safety in wet Age-related Macular Degeneration studies (VIEW 1 and VIEW 2) support this by demonstrating that aflibercept, dosed every 2 months after a monthly loading dose for 3 months, was noninferior in the proportion of patients who maintained or improved vision at 52 weeks compared with monthly injections of ranibizumab. These results were maintained over the 2 years of the studies. Aflibercept (Eylea; Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA and Bayer, Basel, Switzerland) was approved by the FDA for the treatment of neovascular AMD on 18 November 2011.

Keywords: aflibercept, neovascular age-related macular degeneration, ranibizumab, vascular endothelial growth factor, wet age-related macular degeneration

Introduction

In the USA, age-related macular degeneration (AMD) is the leading cause of vision loss in older patients. It is estimated that the prevalence of AMD is 6.5% among people aged 40 years and older [Klein *et al.* 2011]. AMD also remains a leading cause of vision loss among older adults in other Western countries. Most of this vision loss stems from advanced AMD. Advanced AMD can be classified into two major forms: the non-neovascular, atrophic (dry) form or the neovascular (wet) form. The majority of people with severe vision loss (20/200 or worse) from AMD have the neovascular form, which is estimated to occur in 10–20% of patients [Ferris *et al.* 1984]. Currently, there is no effective treatment for advanced, dry AMD [Meleth *et al.* 2011]. However, neovascular AMD has been successfully targeted by a number of treatment strategies.

Overview of current therapy

The hallmark of wet AMD is the formation of new, anomalous blood vessels that typically arise from the choroidal vasculature and can grow into the subretinal pigment epithelial or subretinal space. Rarely, this process may originate from the retina and extend posteriorly into the subretinal space, a form of neovascular AMD termed retinal angiomatous proliferation. These neovascular vessels commonly hemorrhage and leak and can compromise vision by distorting the retinal and subretinal architecture with fluid, blood, or fibrovascular tissue [Spilsbury *et al.* 2000]. Untreated, choroidal neovascularization (CNV) usually leads to permanents loss of central vision.

The pathogenesis of CNV is not completely understood. However, the overexpression of vascular endothelial grown factor (VEGF), a pro-angiogenic cytokine, has been shown to play a crucial role [Spilsbury *et al.* 2000]. Previous studies have demonstrated increased levels of VEGF in the presence of inflammatory cytokines, suggesting that inflammation is a key component of AMD [Nagineni *et al.* 2012]. Others have suggested that ischemia, also associated with increased VEGF [Witmer *et al.* 2003], may play a role in AMD

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[Feigl, 2009]. All of these reports clearly indicate that VEGF is vital to the pathogenesis of CNV in AMD.

Early treatment strategies focused on destruction of choroidal neovascular membranes using laser photocoagulation. The Macular Photocoagulation Study (MPS) established guidelines for treatment of these lesions [Macular Photocoagulation Study Group, 1982, 1986, 1991]. Although this treatment reduced the likelihood of severe vision loss compared with the natural course of the disease, there were many limitations, especially when treating lesions in the fovea. The primary downsides were related to the fact that the laser induced a permanent scotoma, and recurrence of the CNV occurred in over 50% of treated eyes [Macular Photocoagulation Study Group, 1991].

Until 1999, laser photocoagulation was the only treatment for neovascular AMD that had been shown to reduce the risk of vision loss. At that time, the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study reported that photodynamic therapy (PDT) with verteporfin (Visudyne; Novartis Pharma AG, Basel, Switzerland) reduced the risk of moderate to severe vision loss for at least 5 years in patients who presented with subfoveal lesions classified as predominantly classic [TAP Study Group, 1999; Azab *et al.* 2004; Blumenkranz *et al.* 2002; Bressler and TAP Study Group, 2001; Bressler *et al.* 2002; Kaiser *et al.* 2006]. PDT is a two-step process that involves the intravenous injection of verteporfin, a photosensitizing molecule, which is taken up by dividing cells within CNV. The drug is activated by local application of energy from a diode laser source at a wavelength that corresponds to an absorption peak of the molecule. A photochemical reaction occurs and activated free radicals are generated that can lead to capillary endothelial cell damage and vessel thrombosis. At 2 years, 59% of verteporfin treated eyes *versus* 31% of placebo eyes avoided at least moderate vision loss [Bressler and TAP Study Group, 2001]. While PDT improved the results seen with laser photocoagulation, there remained a pressing need for better treatment modalities.

The first VEGF inhibitor to obtain US Federal Drug Administration (FDA) approval for CNV in AMD was pegaptanib (Macugen; OSI/Eyetech Pharmaceuticals, New York, NY, USA) in 2004. Pegaptanib is an RNA aptamer that binds human $VEGF_{165}$ with high affinity and specificity [Gragoudas *et al.* 2004]. The drug, however, did not bind other active VEGF isoforms such as $VEGF_{121}$. Pegaptanib is administered as an intravitreal injection every 6 weeks. The VEGF Inhibition Study in Ocular Neovascularization (VISION) trial was a prospective, randomized, double-masked, controlled, dose-ranging phase III clinical trial in which 1186 patients with AMD and subfoveal CNV received one of three doses of pegaptanib or sham injections every 6 weeks for 48 weeks [Gragoudas *et al.* 2004]. The results of this study were promising, with 70% of patients losing less than three lines of vision compared with 55% of controls ($p < 0.001$). Unfortunately, similar to the results with PDT, a minority of patients gained vision with this therapy.

One of the most exciting advances in the treatment of CNV in AMD came with the introduction of ranibizumab (Lucentis; Genentech, South San Francisco, CA, USA) in 2006. Ranibizumab is a recombinantly produced, humanized, antibody (Fab) fragment that binds VEGF [Rosenfeld *et al.* 2006]. Unlike pegaptanib, ranibizumab binds to and inhibits the biological activity of all active forms of VEGF-A. The Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) study was a randomized, double-masked, sham-controlled clinical trial of 716 patients with minimally classic or occult CNV secondary to AMD treated with one of two different doses of intravitreal ranibizumab or sham injections given every 4 weeks for 2 years [Rosenfeld *et al.* 2006]. The results of this study were revolutionary with 94.5% of patients treated with ranibizumab 0.3 mg and 94.6% of patients treated with ranibizumab 0.5 mg experiencing vision stabilization or improvement compared with 62.2% of patients receiving sham injections ($p < 0.001$). In fact, visual acuity improved by 15 letters or more in 24.8% of patients receiving 0.3 mg and 33.8% of patients receiving 0.5 mg ranibizumab compared with 5.0% of the sham injection group ($p < 0.001$). These results were further supported by the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) study, which was a randomized, controlled, double-masked phase III clinical trial of 423 patients that compared patients treated with ranibizumab with patients treated with PDT with verteporfin treatment [Brown *et al.* 2006, 2009]. These results showed that 94.3% of patients treated with

0.3 mg ranibizumab and 96.4% of patients treated with 0.5 mg ranibizumab lost less than 15 letters of vision compared with 64.3% of patients treated with PDT at 1 year ($p < 0.001$). Patients receiving ranibizumab again showed increased vision in 35.7% of patients treated with 0.3 mg ranibizumab and 40.3% of patients treated with 0.5 mg ranibizumab compared with only 5.6% of patients treated with PDT ($p < 0.001$). The results of these trials resulted in anti-VEGF therapies largely replacing previous treatment modalities.

Bevacizumab (Avastin; Genentech) is a full-length monoclonal antibody that binds all isoforms of VEGF-A. The FDA originally approved it in February 2004 for the treatment of metastatic colorectal cancer. Soon thereafter, physicians started to use it off label as an intravenous or intravitreal treatment for neovascular AMD. Despite the lack of clinical research to support its safety or efficacy, anecdotal evidence led to its widespread popularity prior to the approval of ranibizumab in 2006. To deliver an intravitreal injection, a physician or pharmacy takes a vial of bevacizumab and makes numerous unit doses. This dramatically lowers the cost of the drug. The approximate cost differential between ranibizumab (US$2000) and bevacizumab (US$S50) was prohibitive for some patients, and bevacizumab continued to be utilized, despite not being FDA approved for intravitreal use. In fact, in a review of Medicare claims for neovascular AMD in 2008, it was noted that 58% of all intravitreal injections given were bevacizumab and 41% were ranibizumab [Brechner *et al.* 2011].

To address the safety and therapeutic concerns of the widespread, off-label use of bevacizumab in the treatment of wet AMD, the National Eye Institute commissioned the Comparison of Age-Related Macular Degeneration Treatment Trial (CATT) [CATT Research Group *et al.* 2011]. In this multicenter, single-blind, noninferiority trial, 1208 patients with neovascular AMD were randomized into four groups. After the first mandatory intravitreal injection, patients received ranibizumab every 28 days (ranibizumab monthly), bevacizumab every 28 days (bevacizumab monthly), ranibizumab only when signs of active neovascularization were present (ranibizumab as needed), and bevacizumab only when signs of active neovascularization were present (bevacizumab as needed). The 1-year results of this study demonstrated that monthly bevacizumab was equivalent to monthly ranibizumab with 8.0 and 8.5 letters gained, respectively. Bevacizumab as needed was found to be equivalent to ranibizumab as needed with 5.9 and 6.8 letters gained, respectively. While ranibizumab as needed was found to be equivalent to ranibizumab monthly, the equivalence of bevacizumab as needed compared with bevacizumab monthly was found to be inconclusive.

Aflibercept

Aflibercept (Eylea; Regeneron, Tarrytown, NY, USA and Bayer, Basel, Switzerland) is a fully human, recombinant fusion protein composed of the second immunoglobulin (Ig) binding domain of VEGF receptor 1 and the third Ig binding domain of VEGF receptor 2, fused to the Fc region of human IgG1. It binds to all VEGF-A isoforms, VEGF-B, and placental growth factor (PlGF) [Papadopoulos *et al.* 2012]. Aflibercept is a member of Regeneron's proprietary family of 'Trap' products that catch, hold, and block (i.e. trap) certain cytokines [Adis R&D Profile, 2008]. Aflibercept is being developed for the treatment of cancer (Zaltrap; Regeneron and Sanofi, Bridgewater, NJ, USA) and eye disorders. The eye formulation, also referred to in the literature as VEGF Trap-Eye, is identical in structure to the intravenous cancer treatment, with further purification steps and buffer modification to allow for comfortable, nonirritating intravitreal injection [Dixon *et al.* 2009].

Unlike currently available anti-VEGF therapies, aflibercept binds PlGF in addition to all isoforms of VEGF-A and VEGF-B. Like VEGF, PlGF is present in human CNV membranes, and animal studies have shown that PlGF contributes to the development of experimental CNV [Rakic *et al.* 2003]. Another differentiating feature of aflibercept is that the binding affinity for VEGF is 0.5 pM Kd, which is considerably stronger than ranibizumab, bevacizumab, or native VEGF receptors. This allows for effective blocking of VEGF, even at low concentrations, which may translate into a longer duration of action and extended dosing intervals [Stewart and Rosenfeld, 2008].

The results of preclinical studies were promising. In Matrigel-induced models of CNV in rats, aflibercept was shown to arrest the growth of CNV and led to the regression of recently established lesions [Cao *et al.* 2010]. Primate studies of laser-induced CNV also showed promise for the drug. When aflibercept was given prior to and following

attempted laser induction of CNV, minimal neovascularization was noted compared with placebo. In drug-naïve eyes with previously established CNV, aflibercept was successful in causing regression of the CNV and resolving vascular leakage [Nork *et al.* 2011]. These encouraging results coupled with the apparent safety of the drug, fueled the demand for human clinical trials.

Phase I

A phase I, randomized, multicenter, masked, placebo-controlled clinical trial of *intravenous* aflibercept in patients with subfoveal CNV from AMD showed a dose-dependent decrease in retinal thickness [Nguyen *et al.* 2006]. However, at systemic doses of 3 mg/kg, hypertension and proteinuria were observed, and the study was halted for safety concerns. This led to investigation of alternative delivery methods.

The safety, tolerability, maximum tolerated dose, and bioactivity of intravitreal injection of aflibercept were evaluated in a phase I, multicenter, dose-escalation study [Nguyen *et al.* 2009]. In the study, 21 patients received a single dose of aflibercept. Patients were monitored for 12 weeks after injection. There were no serious ocular or systemic events noted. With any dose of aflibercept, stable or improved vision was seen in 95% of patients at 6 weeks. The mean decrease in foveal thickness was −105.5 μm, and the mean increase in visual acuity was +4.43 letters. Half of the patients receiving 2 or 4 mg doses showed no retinal leakage and maintained vision gains at 12 weeks after a single injection. These positive results paved the way for further development of an intravitreal formulation of aflibercept.

Phase II

The clinical evaluation of anti-angiogenesis in the retina study (CLEAR-IT) 2 trial was a phase II multicenter, prospective, randomized, double-masked clinical trial designed to study the effect of intravitreal aflibercept in patients with neovascular AMD [Brown *et al.* 2011; Heier *et al.* 2011]. This trial was divided into two parts. In the first part, patients were treated with a fixed dosing interval up to 12 weeks. The second part of the study was designed to be as needed (PRN) dosing and took place from week 16 to 52. The primary endpoint of the study was the change in central retinal thickness. The mean change in best corrected visual acuity (BCVA) was evaluated as a secondary outcome. The study included 159 patients who were randomized into five treatment groups. The first two groups received treatment every 4 weeks and were dosed at 0.5 mg (group 1) or 2 mg (group 2). The last three groups were treated every 12 weeks and were dosed at 0.5 mg (group 3), 2 mg (group 4), or 4 mg (group 5). The primary outcome was at 12 weeks, following the fixed dosing period. The mean decrease in central retinal thickness from baseline to 12 weeks in all groups was −119 μm. Monthly dosing with either 0.5 or 2 mg (groups 1 and 2) provided a more profound and consistent effect than any of the groups treated every 12 weeks. Overall, there was a mean increase in BCVA of +5.7 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in all groups. The greatest mean increase in BCVA, more than +8 letters, was seen in the monthly dosing groups compared with the patients receiving only one injection [Brown *et al.* 2011].

For the PRN dosing arm of the study, patients were evaluated every 4 weeks to determine the need for continued treatment. Patients received an injection of the baseline dose at week 12. At week 16 and thereafter, eyes were reinjected with aflibercept if any of the following conditions were noted: increase in central retinal thickness of at least 100 μm by optical coherence tomography (OCT); loss of at least 5 ETDRS letters with recurrent fluid on OCT; persistent fluid on OCT; new-onset of classic CNV; new or persistent leak on fluorescein angiography; or new macular hemorrhage on clinical examination. Using these criteria, the mean decrease in central retinal thickness in all groups from baseline to 52 weeks was −130 μm. The mean increase in BCVA was +5.3 ETDRS letters in all groups. The greatest increase in BCVA occurred in the group initially treated with 2 mg every 4 weeks for 12 weeks before PRN dosing with a mean increase of +9.0 letters at 1 year. To achieve these excellent visual gains, an average of two additional injections was administered after the 12-week fixed-dosing phase across all groups. The mean time to the first reinjection was 129 days, with 19% of patients receiving no injections and 45% receiving one or two additional injections [Heier *et al.* 2011].

Phase III

Two parallel, phase III, double-masked, randomized studies were initiated in August 2007. The VEGF Trap-Eye: Investigation of Efficacy and Safety in wet Age-Related Macular Degeneration

Table 1. Summary of the 1-year results of VIEW 1 and VIEW 2 studies compared with MARINA and CATT trials.

	MARINA		CATT		VIEW 1 (12 months)				VIEW 2 (12 months)			
	Ran 0.5 mg	Sham	Ran 0.5 mg	Bev 0.5 mg	Afl 0.5 mg	Afl 2 mg	Afl 2 mg Q*	Ran 0.5 mg	Afl 0.5 mg	Afl 2 mg	Afl 2 mg Q*	Ran 0.5 mg
≥15 letter gain (%)	33	4	34	31								
Stable vision (%)	90	53	94	94	96	95	95	94	96	96	96	94
Mean gain in VA from baseline at 12 months	+7.2	−10.4	+8.5	+8.0	+8.1	+10.9	+7.9	+8.1	+9.7	+7.6	+8.9	+9.4
Number of injections	12		12	12								

*Dosed every 8 weeks after treatment initiation with 3 monthly doses.
Afl, aflibercept; Bev, bevacizumab; CATT, Comparison of Age-Related Macular Degeneration Treatment Trial; MARINA, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD; Ran, ranibizumab; VA, visual acuity; VIEW, VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet Age-related Macular Degeneration.

(VIEW 1) study was performed in North America. The VIEW 2 study was an international study including Europe, Asia Pacific, Japan, and Latin America. The studies were designed as noninferiority studies comparing intravitreal aflibercept with ranibizumab. Patients with subfoveal CNV due to AMD were randomized into four groups. The first two groups received intravitreal injections of aflibercept at doses of 0.5 and 2 mg administered at 4-week intervals. The third group received 2 mg of aflibercept at 8-week intervals following three loading doses given every 4 weeks. These were compared with the fourth group, the control, receiving 0.5 mg of ranibizumab administered every 4 weeks. The primary endpoint was statistical noninferiority in the proportion of patients who maintained or improved vision over 52 weeks compared with ranibizumab.

The 1-year results of the VIEW 1 study showed that vision was maintained, defined as losing fewer than 15 ETDRS letters, in 96% of patients receiving aflibercept 0.5 mg monthly, 95% of patients receiving 2 mg monthly, and 95% of patients receiving 2 mg every 2 months. These results compared favorably with the 94% of patients maintaining vision in the group receiving ranibizumab 0.5 mg monthly [Regeneron, 2010; Heier, 2011]. The patients receiving aflibercept 2 mg monthly on average gained 10.9 letters compared with a mean 8.1 letter gain with ranibizumab 0.5 mg dosed every month ($p < 0.01$). The VIEW 2 study showed similar results, with maintenance of vision in 96% of patients receiving 0.5 mg monthly, 96% of patients receiving 2 mg monthly, and 96% of patients receiving 2 mg every 2 months. These results also compared favorably with the 94% of patients maintaining vision in the group treated with ranibizumab 0.5 mg monthly [Schmidt-Erfurth, 2011]. They are similar to results found in the MARINA and CATT trial (Table 1). The safety of both VIEW 1 and VIEW 2 studies was excellent with no difference seen between any aflibercept group and the ranibizumab group. The fact that 2 mg aflibercept dosed every 8 weeks after three loading doses was noninferior to ranibizumab dosed every 4 weeks in terms of safety and efficacy is exciting, as it offers the hope of similar visual gains with less treatment burden.

The 2-year results of the VIEW 1 and VIEW 2 studies were recently released [Regeneron, 2011]. The integrated analysis of these two studies (Table 2) shows that patients receiving aflibercept 2 mg every 8 weeks gained +7.6 letters from baseline at week 96 compared with +8.4 letters at week 52. The visual acuity gain in from baseline in patients receiving monthly ranibizumab was +7.9 letters at week 96 compared with +8.7 letters at week 52. Patients receiving aflibercept 2 mg every 8 weeks received an average of 11.2 injections over 2 years while patients treated with ranibizumab had an average of 16.5 injections over 2 years. Aflibercept (Eylea) was approved by the FDA for the treatment of wet AMD on 18 November 2011.

Conclusions

The evolution of treatment strategies for neovascular AMD has resulted in a paradigm shift in terms of expectations among patients and physicians. Prior to these recent advances, patients

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