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REVIEW

Aflibercept in wet AMD: specific role and optimal use

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Background: Vascular endothelial growth factor (VEGF) is a naturally occurring glycoprotein in the body that acts as a growth factor for endothelial cells. It regulates angiogenesis, enhances vascular permeability, and plays a major role in wet age-related macular degeneration. The consistent association between choroidal neovascularization and increased VEGF expression provides a strong reason for exploring the therapeutic potential of anti-VEGF agents in the treatment of this disorder. Blockade of VEGF activity is currently the most effective strategy for arresting choroidal angiogenesis and reducing vascular permeability, which is frequently the main cause of visual acuity deterioration. In recent years, a number of other molecules have been developed to increase the efficacy and to prolong the durability of the anti-VEGF effect. Aflibercept (EYLEA®; Regeneron Pharmaceutical Inc and Bayer), also named VEGF Trap-eye, is the most recent member of the anti-VEGF armamentarium that was approved by the US Food and Drug Administration in November 2011. Because of its high binding affinity and long duration of action, this drug is considered to be a promising clinically proven anti-VEGF agent for the treatment of wet maculopathy.

Objective: This article reviews the current literature and clinical trial data regarding the efficacy and the pharmacological properties of VEGF-Trap eye and describes the possible advantages of its use over the currently used "older" anti-VEGF drugs.

Methods: For this review, a search of PubMed from January 1989 to May 2013 was performed using the following terms (or combination of terms): vascular endothelial growth factors, VEGF, age-related macular degeneration, VEGF-Trap eye in wet AMD, VEGF-Trap eye in diabetic retinopathy, VEGF-Trap eye in retinal vein occlusions, aflibercept. Studies were limited to those published in English.

Results and conclusion: Two Phase III clinical trials, VEGF Trap-eye Investigation of Efficacy and Safety in Wet AMD (VIEW) 1 and 2, comparing VEGF Trap-eye to ranibizumab demonstrated the noninferiority of this novel compound. The clinical equivalence of this compound against ranibizumab is maintained even when the injections are administered at 8-week intervals, which indicates the potential to reduce the risk of monthly intravitreal injections and the burden of monthly monitoring.

Keywords: aflibercept, AMD, neovascularization, VEGF, VEGF inhibition, VEGF-Trap eye

Introduction

The neovascular form of age-related macular degeneration (AMD), also known as wet AMD, is characterized by the formation of subretinal choroidal neovascularization (CNV) and is the cause of most cases of blindness in the elderly. Wet AMD is the major cause of severe vision loss in developed nations and is estimated to affect >2.5 million people worldwide.[1,2] The patients affected by exudative AMD often experience rapid

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loss of fine resolution central vision over several months, and early visual stabilization is a key issue in preserving visual acuity.[3]

Vascular endothelial growth factor (VEGF) is a naturally occurring glycoprotein in the body that acts as a growth factor selective for endothelial cells. It regulates angiogenesis, enhances vascular permeability, and plays a leading role in wet AMD. The consistent association between CNV and increased VEGF expression provides a strong reason for exploring the therapeutic potential of anti-VEGF agents for the treatment of this disorder.[4] Blockade of VEGF actions is currently the most effective strategy in arresting choroidal angiogenesis and reducing vascular permeability, which is frequently the main cause of visual acuity deterioration.[5]

Although pegaptanib (Macugen®; Eyetech Pharmaceuticals Inc, FL, USA and Pfizer Inc, New York, NY, USA) was the first VEGF inhibitor approved by the US Food and Drug Administration (FDA). Important advances in the on-label treatment of CNV in AMD have been achieved with the introduction of ranibizumab (Lucentis; Genentech USA, Inc, San Francisco, CA, USA) in 2006. The off-label use of bevacizumab (Avastin; Genentech USA, Inc) has also shown efficacy for treating wet AMD and other exudative retinal diseases and despite the lack of clinical trials to support its safety or efficacy, anecdotal evidence led to its widespread popularity prior to the approval of ranibizumab.

Aflibercept (EYLEA®; Regeneron Pharmaceutical Inc, Tarrytown, NY, USA and Bayer, Basel, Switzerland), also named VEGF Trap-eye, is the most recent member of the anti-VEGF family. This drug has been recently developed to afford a more potent and prolonged anti-VEGF effect and was approved by the FDA in November 2011.[6] This article reviews the efficacy and summarizes the pharmacological properties of VEGF Trap-eye and describes the possible advantages of its use over the currently used "older" anti-VEGF drugs.

Overview of VEGF and its pathological effects in neovascular AMD

VEGF-A (usually simply referred to as VEGF) is a growth factor encoded by a gene family that also includes placental growth factor (PIGF), VEGF-B, VEGF-C, VEGF-D, and the orf virus encoded VEGF-E.[7] Differences in exon splicing result in the generation of four main VEGF isoforms: $VEGF_{121}$, $VEGF_{165}$, $VEGF_{189}$, and $VEGF_{206}$, which have 121, 165, 189, and 206 amino acids after cleavage of the signal sequence, respectively.[8]

VEGF stimulates the growth of vascular endothelial cells derived from arteries, veins, and the lymphatic system.[9] It also induces the formation of thin-walled endothelium-lined structures (ie, angiogenesis) in a variety of in vivo models,[10] and induces rapid elevations in microvascular permeability.[11] VEGF acts also as a survival factor for endothelial cells, both in vitro and in vivo.[12,13] Although endothelial cells represent the primary target of VEGF, several studies have demonstrated that VEGF has mitogenic effects on nonendothelial cell types[14] and promotion effects on monocyte migration.[15] VEGF protects neurons from insults such as hypoxia and glutamate toxicity[16] and it stimulates neurogenesis in vitro and in vivo.[17]

VEGF contributes mainly at the initiation stage of CNV by promoting both angiogenesis and vasculogenesis. It acts as an endothelial cell specific mitogen as part of the angiogenesis pathway, and also as a chemoattractant for endothelial cell precursors, inducing their mobilization and differentiation in the vasculogenesis pathway.[16] In addition to these activities, VEGF affects vascular permeability by inducing formation of pores in vascular endothelial cells[17,18] and by disrupting the intercellular junction between these cells.[19] In turn, this leads to extravasation of fluid, proteins, and circulating cells which disrupts the retinal anatomy and separates the retina from underlying structures, potentially causing severe vision loss.

Although other growth factors can induce the development of blood vessels (ie, transforming growth factor-β, interleukins, insulin-like growth factor-1, and epidermal growth factor), only VEGF appears to be both sufficient and essential for physiologic and pathologic angiogenesis. For this reason, the biochemical pathways involving VEGF are the most studied targets for new potential drugs against neovascular pathologies. Anti-VEGF therapy can arrest choroidal angiogenesis and reduce vascular permeability, which is frequently the main cause of visual acuity deterioration. Pegaptanib and ranibizumab have been approved by the FDA for the treatment of wet AMD, and the off-label use of a third agent, bevacizumab, has shown efficacy for treating wet AMD and other exudative retinal diseases. Pegaptanib was the first anti-VEGF drug FDA approved in December 2004.[20–22] However, because it was proven to be less efficacious than other anti-VEGF drugs, possibly owing to its selective binding of $VEGF_{165}$, it is no longer widely used in most countries. Ranibizumab and bevacizumab, which are nonselective anti-VEGF drugs, are currently the most extensively used drugs worldwide for wet AMD as well as for many other ocular diseases in which VEGF is overexpressed.[23]

The development of new agents for wet AMD has focused on both improving efficacy and extending the duration of action in comparison with the commonly used anti-VEGF drugs ranibizumab and bevacizumab, which are considered the standard drugs. Ranibizumab is a monoclonal humanized antibody fragment and bevacizumab is a whole monoclonal antibody, and both show a high binding affinity for all isoforms of VEGF. These agents appear to have similar efficacy profiles and mechanisms of action, ie, they block the extracellular availability of VEGF which can arrest choroidal angiogenesis and reduce vascular permeability for a limited period of time.[24–27]

Bevacizumab has a lower binding affinity for VEGF than ranibizumab.[28] However, bevacizumab is approximately three times larger than ranibizumab (149 kDa versus 48 kDa), and its substantially higher molecular weight results in an intravitreal half-life that is 36% higher than that of ranibizumab. Accumulating clinical evidence has demonstrated that the effects of a single intravitreal dose of either bevacizumab or ranibizumab effectively reduces the effect of VEGF on CNV for 4–6 weeks in most eyes.[29,30]

Ranibizumab, which is the only widely used drug that is currently approved by the FDA for the treatment of neovascular AMD, is most extensively studied. Several ranibizumab Phase III clinical trials that have studied different treatment schedules, doses, and populations have obtained good results with monthly injections, ie, a mean number of 25 intravitreal injections over 2 years.[31,32]

Despite the off-label status of bevacizumab, however, it is preferred over ranibizumab by nearly 60% of physicians[33] because of its significantly lower price (ranibizumab, US $1,950 versus bevacizumab, US $50) and similar efficacy. The FDA originally approved bevacizumab in 2004 for the treatment of metastatic colorectal cancer.[34] To deliver an intravitreal injection, the physician or pharmacist makes numerous unit doses from a vial of bevacizumab, dramatically lowering the cost of the drug. Moreover, many reports and a 2-year multicenter, randomized clinical trial (the Comparisons of Age-Related Macular Degeneration Treatment Trial [CATT]) demonstrated its near equivalency to ranibizumab with monthly dosing (+7.8 letters versus +8.8 letters) and insignificant poorer outcomes with as-needed dosing (+5.0 versus +6.7 letters).[24,25] Moreover, while the systemic half-life of the unbound product of bevacizumab (20 days) was longer than that of ranibizumab (6 hours), severe systemic adverse events occurred at similar frequencies in patients receiving bevacizumab and ranibizumab in the CATT trial.[26,35,36]

The main problem with the current anti-VEGF therapy is that monthly intravitreal injections are required for maintaining vision. This necessitates an excessive time commitment from patients and institutions, and increases the physical and psychological discomfort and financial burdens for the patients. On the other hand, evidence from the SAILOR (Safety Assessment of Intravitreous Lucentis fOR AMD),[37] PIER (A Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization [CNV] with or without Classic CNV Secondary to Age-Related Macular Degeneration),[38,39] and EXCITE (Efficacy and Safety of Ranibizumab in Patients With Subfoveal Choroidal Neovascularization [CNV] Secondary to Age-Related Macular Degeneration)[40] studies indicates that the efficacy decreases if treatment frequency is reduced. After the loading dose of monthly injections for 3 months of ranibizumab, vision decreases or returns to baseline in most patients if the frequency is reduced to one injection every 2, 3, or 4 months.

Although monthly injections of anti-VEGF represent the best way to preserve vision, most retina surgeons use individualized treatment protocols with monthly assessments after the first three intravitreal injections of anti-VEGF, and further injections are given only if signs of disease activity persist as observed on optical coherence tomography (OCT). This strategy is also abbreviated as "PRN dosing" from the Latin phrase Pro Re Nata, which means "as circumstances arise." The PrONTO (Prospective Optical Coherence Tomography [OCT] Imaging of Patients With Neovascular AMD Treated With Intra-Ocular Ranibizumab) study used this strategy and obtained visual outcomes similar to those achieved with monthly injections while reducing the number of injections from 25 to 10 over 2 years.[41] However, even with this dosing regimen, patients are still required to make monthly visits to the office and undergo frequent and expensive testing because of the constant risk of CNV recurrence.

A treatment approach that aims to reduce the number of injections and the number of visits is the "treat and extend" method. It consists of 3 monthly injections and a follow-up examination after 6 weeks. If the follow-up examination shows evidence of exudation, the patient is treated and told to undergo a follow-up examination in 4 weeks, otherwise the patient is still treated but the follow-up period is extended to 8 weeks. A similar evaluation is performed at the next follow-up visit. However, there is not much evidence in favor of this treatment method. Thus, research on new compounds is focused on inhibiting the VEGF signaling pathway for a more prolonged period.[1]

Aflibercept (EYLEA®; Regeneron Pharmaceutical Inc and Bayer), or VEGF Trap-eye, is a novel compound derived from the native VEGF receptor (VEGFR) that binds to all VEGF and VEGF-B isoforms as well as to PlGF.[42] VEGF Trap-eye promises to decrease the injection frequency in conjunction with the "treat and extend" or "PRN" strategies and appears to serve as an effective alternative drug for patients who are less responsive to the previously approved anti-VEGF drugs.

Structure and mechanism of action

The FDA approved VEGF Trap-eye (EYLEA®, Regeneron Pharmaceutical Inc, and Bayer) for the treatment of subfoveal CNV caused by wet AMD on November 18, 2011.[43] VEGF Trap-eye is an intraocular formulation of aflibercept, a product used in oncology (Zaltrap; Regeneron Pharmaceutical Inc), that has been specifically purified and buffered to minimize the risk of eye toxicity when injected intravitreally.[44] It is a fully human, recombinant fusion protein that has the property to "trap," that is to catch, hold, and block certain molecules. Aflibercept was constructed from portions of the human VEGFR fused to the FC portion of a human IgG1.[45]

Circulating VEGF initiates a biochemical cascade by activating three membrane spanning tyrosine kinase receptors: VEGFR-1, VEGFR-2, and VEGFR-3.[46,47] VEGFR-1 (fms-like tyrosine kinase-1, Flt-1) was the first VEGF receptor identified more than a decade ago.[48] VEGFR-1 releases tissue specific growth factors, recruits endothelial progenitors, and induces matrix metalloproteinases. It is thought to modulate VEGFR-2 signaling and to act as a dummy/decoy receptor by sequestering VEGF and preventing it from binding to VEGFR-2.[7] VEGFR-2 (kinase insert domain-containing receptor or KDR) is considered the major mediator of the mitogenic, angiogenic, permeability enhancing, and anti-apoptotic effects of VEGF.[7]

Both VEGFR-1 and VEGFR-2 have seven Ig-like binding sequences for VEGF (two of which are incorporated in VEGF Trap-eye) in the extracellular region, a single transmembrane region, and a consensus tyrosine kinase sequence that is interrupted by a kinase insert domain.[49–51] The third member of the same family of receptor tyrosine kinases is VEGFR-3.[52] This protein is not a receptor for VEGF, but binds VEGF-C and VEGF-D.[53] Because VEGFR-1 possesses a higher affinity for VEGF than VEGFR-2, drug developers have used its binding sequences for VEGF Trap-eye.

Structurally, aflibercept is a soluble decoy receptor of 115 kDa that is made by the second binding domain of VEGFR-1 and the third binding domain of VEGFR-2, which then are fused to the FC region of a human IgG1 (Figure 1).

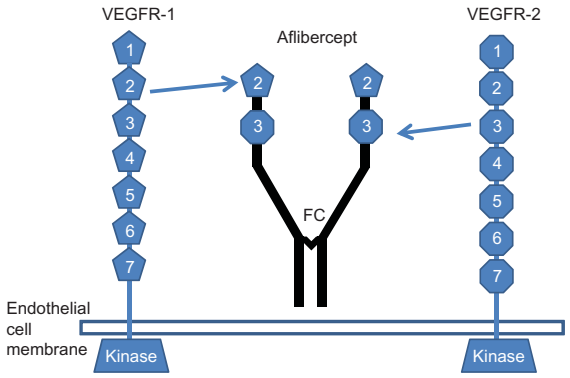

Figure 1 Diagram showing the structure of the vascular endothelial growth factor receptor-1 and -2 and the structure of aflibercept (VEGF Trap-eye).
Notes: Aflibercept (VEGF Trap-eye) is generated by a fusion that includes the second binding domain of vascular endothelial growth factor receptor (VEGFR)-1 and the third binding domain of VEGFR-2 attached to a FC fragment of a human IgG.
Abbreviation: FC, fragment crystallizable region.

The intermediate size of aflibercept (115 kDa compared to 48 kDa for ranibizumab and 148 kDa for bevacizumab) results in an estimated intravitreal half-life of 7.1 days and a duration of clinical action possibly as long as 2.5 months, which exceeds the 1-month intravitreal binding activity of ranibizumab.[54,55] The molecular configuration of aflibercept allows it to bind to all of the VEGF isoforms more tightly than their native receptors (the dissociation constant [K_d] of aflibercept for $VEGF_{165}$ = 0.49 pmol/L).[42] Thus, this compound effectively prevents VEGF from binding and activating its cognate receptors (the K_d of VEGFR-1 and VEGFR-2 for $VEGF_{165}$ are 9.33 and 88.8 pmol/L,

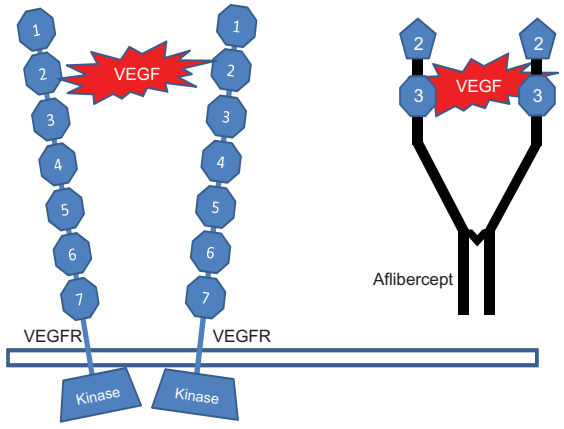

Figure 2 Vascular endothelial growth factor binds to two vascular endothelial growth factor receptors which induces the angiogenic response by activating the tyrosine kinase.
Notes: Vascular endothelial growth factor receptor (VEGFR)-2 is shown. Aflibercept (VEGF Trap-eye) binds all vascular endothelial growth factor (VEGF) isoforms more tightly than their native receptors, thus preventing binding of VEGF to its cognate receptors.

respectively) (Figure 2).[56] Moreover, the binding affinity of aflibercept (K_d = 0.49 pmol/L) is almost 100 times higher than that of ranibizumab (K_d = 46 pmol/L) and bevacizumab (K_d = 58 pmol/L).[54,55] This was primarily attributed to the association rate constant for aflibercept binding to human $VEGF_{165}$, which is almost 80 times faster than the corresponding association rate constant values for ranibizumab and bevacizumab.

Because of these characteristics, the ability of aflibercept to block VEGF induced activation of VEGFR-1 and -2 in vitro is much stronger than that of ranibizumab and bevacizumab. Additionally, it blocks both PlGF-1 and PlGF-2 mediated activation of VEGFR-1, whereas ranibizumab and bevacizumab do not show such activity. A presumably important functional difference between aflibercept and the other anti-VEGF drugs currently in use is that it can bind and inhibit VEGF as well as PlGF-1 and -2 and VEGF-B, which have also been implicated in pathological vascular remodeling. Experimental evidence shows that targeting VEGF-B and PlGF inhibits CNV and suggests that PlGF synergizes with VEGF in promoting vascular pathology in wet AMD.[57]

Pharmacodynamics, pharmacokinetics, and metabolism

Aflibercept forms a stable, inert 1:1 complex with either VEGF, VEGF-B, or the PlGF ligand preventing the activation of their receptors, VEGFR-1 and -2.[56] The highest intravitreal dose used in pivotal trials for aflibercept is 2 mg, which is 100-fold lower than the dose allowed in oncology (4–6 mg/kg).[44,60] Following intravitreal injection of 2 mg of aflibercept, the drug can be detected in plasma as a free drug (a minor quantity) or in a complex bound with VEGF. The drug is rapidly cleared from circulation via pinocytotic proteolysis and glomerular filtration after forming a complex with VEGF via the same pathways that metabolize antibodies.

Following intravitreal injection of 2 mg of aflibercept, the mean maximal plasma concentration of unbound VEGF Trap-eye is attained in 1–3 days, and was estimated to be 200-fold lower than the concentration required for maximal systemic VEGF binding. The systemic half-life of unbound aflibercept is 1.5 days, which is inferior to that of bevacizumab (20 days) and closer to the systemic half-life of ranibizumab (6 hours).[59] Free aflibercept has never been detected in plasma at 2 weeks after intravitreal injection and cannot accumulate in plasma in the loading phase.[44] Thus, an intravitreal aflibercept dose of 2 mg would be predicted to cause negligible systemic activity and have a systemic safety profile similar to that of ranibizumab.

Therapeutic efficacy

The first surveys regarding the use of aflibercept in treatment of wet AMD emerged from a preclinical study conducted on animal models. This study, published in 2003, showed the first evidence that VEGF Trap-eye is capable of suppressing CNV and VEGF mediated breakdown of the blood–retinal barrier in transgenic mice with laser induced CNV, which was treated with subcutaneous or intravitreal administration.[58] The initial use of aflibercept for wet AMD consisted of intravenous injections with doses between 0.3 mg/kg and 3 mg/kg (the usual oncologic dose is 4 mg/kg) and administered every 2 weeks to 25 patients.[60] Macular thickness decreased by an average of 66% and vision improved in many patients. Patients receiving the higher dose (3 mg/kg) experienced more systemic hypertension and proteinuria than those treated with the lower dose (1 mg/kg). However, the promising effects obtained intravenously encouraged researchers to transition the trial to intravitreal injections.

The Phase I Clinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trial (CLEAR-IT 1)[60] investigation was a small trial (21 patients) designed to determine the maximum tolerated dose, the bioactivity, and the safety and tolerability of intravitreally administered aflibercept in patients with wet AMD. This study confirmed that aflibercept doses between 0.05 mg and 4 mg were well tolerated. At 6 weeks after a single injection, most patients experienced an improvement in visual acuity (mean visual gain, 4.4 letters) and showed a decrease in macular thickness (−105 μm). Almost 50% of the patients followed for 12 weeks did not show retinal leakage and maintained vision gain.[61,62] On the basis of the results of CLEAR-IT 1, the developers hoped to show that an intravitreal formulation of aflibercept could be administered less frequently than once a month.

In a Phase II dose and interval ranging trial, 159 patients with wet AMD (CLEAR-IT 2) were randomized into five treatment groups: the first two groups received 3 monthly aflibercept injections of 0.5 mg or 2 mg and the other three groups received only one aflibercept injection of 0.5 mg, 2 mg, or 4 mg.[64] Final global evaluations were performed at 12 weeks. Although visual improvement at week 8 was similar in patients receiving a single dose or two doses (5.7 letters), the average vision in all groups improved more in patients treated monthly (mean gain of ≥8 letters) at 12 weeks. After 12 weeks, the reduction in macular thickness experienced by the patients receiving three monthly injections

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