Antivascular endothelial growth factor therapy for neovascular age-related macular degeneration

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Purpose of review

The most important recent advance in the treatment of neovascular age-related macular degeneration (AMD) is the development of antivascular endothelial growth factor (anti-VEGF) therapeutic agents that preserve and improve visual acuity by arresting choroidal neovascular growth and reducing vascular permeability. This review describes the current literature on the use of this therapeutic approach in the management of neovascular AMD.

Recent findings

Two anti-VEGF agents, pegaptanib sodium and ranibizumab, are currently approved by the United States Food and Drug Administration for the treatment of neovascular AMD. In addition, off-label use of a third anti-VEGF agent, bevacizumab, as a treatment option for neovascular AMD has become common worldwide. Other anti-VEGF agent strategies that have shown efficacy include small interfering RNA agents to silence the *VEGF* gene and receptor and the fusion protein VEGF trap.

Summary

The accumulation of preclinical and clinical evidence implicating VEGF-A in the pathogenesis of neovascular AMD has provided a strong rationale for the development of anti-VEGF agents for this disease. Anti-VEGF therapies have been used successfully in the clinic, encouraging their use in the treatment of other neovascular eye diseases.

Keywords

bevacizumab, macular degeneration, neovascularization, pegaptanib sodium, ranibizumab

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Introduction

Ocular diseases involving neovascularization, including neovascular age related macular degeneration (AMD), diabetic retinopathy, diabetic macular edema (DME), and retinal vein occlusion (RVO), are the primary causes of clinically significant vision loss in the developed world [1 3], particularly among the working and elderly popu lations. In the United States, neovascular AMD affects 1.75 million individuals aged more than 40 years and is the leading cause of blindness in those over 65 years [4]. It is characterized by the growth of choroidal blood vessels through Bruch's membrane into the subretinal pigment epithelial (RPE) space, usually leading to accumulation of fluid in the sub RPE space and detachment of the RPE [5].

Inhibition of angiogenesis

Normal and pathologic angiogenesis is a complex balance of positive and negative regulators, and vascular endo thelial growth factor A (VEGF A; also referred to as VEGF) is one of the most important positive regulators of angiogenesis [6] and vascular permeability [7,8]. VEGF A has been implicated in the pathogenesis of a variety of disorders including neovascular AMD, prolif erative diabetic retinopathy (PDR), and other neovascu lar eye diseases, as well as in tumorigenesis. Therefore, VEGF inhibition may be expected to lead not only to inhibition of further angiogenesis but also to regression of newly formed blood vessels.

Therapeutic agents that inhibit VEGF A pegaptanib sodium (Macugen; OSI/Eyetech, Inc., Melville, New York, USA) and ranibizumab (Lucentis; Genentech, Inc., South San Francisco, California, USA) are Food and Drug Administration (FDA) approved for the treat ment of choroidal neovascularization (CNV) secondary to AMD. Of the two agents, ranibizumab offers substantial clinical benefit in neovascular AMD. A third anti VEGF agent, bevacizumab, has been used off label for neovas cular AMD and other exudative retinal diseases. These anti VEGF agents, as well as others in clinical develop ment, have great potential to treat eye diseases character ized by neovascularization. Here, we present an overview of the current knowledge on anti VEGF therapies in neovascular AMD.

Vascular endothelial growth factor-A in vascular permeability, inflammation, and ocular disease

In the various pathologic conditions in which it is implicated, overexpression of VEGF A has been found to promote angiogenesis by inducing endothelial cell proliferation, migration, and survival [9].

Vascular endothelial growth factor-A isoforms

VEGF A is a member of the VEGF family of growth factors that also includes VEGF B, VEGF C, VEGF D, and placental growth factor (PlGF), which have different binding affinities for the three VEGF receptors, VEGFR1, VEGFR2, and VEGFR3 [10,11]. VEGF A also binds to neuropilin 1, a membrane protein on developing neurons that plays a role in embryonic neural blood vessel formation as well as neural tip guidance [12,13]. Alternative RNA splicing of the human *VEGF A* gene results in the formation of four major isoforms ($VEGF_{121}$, $VEGF_{165}$, $VEGF_{189}$, and $VEGF_{206}$) and at least five minor isoforms ($VEGF_{145}$, $VEGF_{148}$, $VEGF_{162}$, $VEGF_{165b}$, and $VEGF_{183}$) [14–16]. $VEGF_{165}$ and $VEGF_{121}$ have been suggested to have the strongest mitogenic and vascular permeability promoting potential [17–19].

Vascular endothelial growth factor-A and vascular permeability

In addition to promoting angiogenesis, VEGF A also affects vascular permeability by inducing formation of pores in the vascular endothelial cells [20] and by disrupting the intercellular junction between these cells [21]. The angiogenic and vascular permeability effects of VEGF A on the endothelium are mediated by the transmembrane receptor VEGFR2 [flk 1/kinase insert domain receptor (KDR)] and involve diverse downstream signaling partners, such as Src family kinases and/or protein tyrosine phosphatases, disrupting and uncoupling the endothelial cell cell junctions [22]. This, in turn, leads to extravasation of fluid, proteins, and circulating cells [22]. In neovascular ocular diseases, the edema from new, permeable blood vessels can disrupt the retinal anatomy and separate the retina from underlying structures, potentially causing severe vision loss.

Vascular endothelial growth factor-A and inflammation

Chronic inflammation occurs in response to infection, autoimmune disease, injury, tumors, and other diseases and involves the release of various cytokines at specific sites in the body by inflammatory cells such as T cells, B cells, macrophages, natural killer cells, neutrophils, and granulocytes. The proinflammatory cytokines include tumor necrosis factor (TNF) α, interleukin (IL) 6, IL 8, and IL 1α, IL 1β, and oncostatin M, which participate in a cascade of events leading to increased levels of VEGF A, promotion of local angiogenesis, and increasing the severity of inflammation.

Vascular endothelial growth factor-A and neovascular ocular diseases

Evidence from preclinical and clinical studies implicates VEGF A in the pathogenesis of neovascular eye diseases. In streptozotocin induced diabetic rats, *VEGF A* gene expression was significantly increased in the ganglion and inner nuclear retinal cell layers compared with control rats [23]. Laser induced RVO in rabbits [24] and monkeys [25] also led to increased VEGF A mRNA expression; VEGF A protein expression was localized to ischemic regions of the retinal layers affected by laser treatment [24]. Furthermore, VEGF A inhibition prevented retinal neovascularization in an ischemia induced mouse model [26] and iris neovascularization in a monkey model [27]. VEGF A inhibition also prevented laser induced CNV in monkeys or shortened its duration [28].

In clinical studies, increased VEGF A expression was found in the RPE [29], subfoveal fibroblasts [30], and surgically excised CNV membranes [31] from eyes of neovascular AMD patients. VEGF A is also overexpressed in the aqueous and vitreous fluid of patients with subretinal neovascularization, diabetic retinopathy, central RVO (CRVO), branch RVO (BRVO), iris neovascularization, retinal detachment, and retinopathy of prematurity (ROP) [32–35] and in all retinal nuclear layers of ischemic CRVO eyes [36]. The consistent association of pathologic ocular neovascularization with increased VEGF A expression provides a strong rationale for exploring the therapeutic potential of anti-VEGF agents in neovascular AMD.

Genetic case–control studies [37] have shown that the *VEGF* gene may influence an individual's tendency to develop AMD. Analyses of single nucleotide polymorphisms (SNPs) in the VEGF A promoter and gene have associated specific VEGF A haplotypes with neovascular AMD [38]. In particular, the VEGF SNP 936C/T [when present with the complement factor H (CFH) Y402H] has been associated with an increased risk of developing wet AMD [39••].

Antivascular endothelial growth factor therapies in neovascular age-related macular degeneration

Intravitreal pegaptanib sodium, an RNA aptamer that targets $VEGF_{165}$ and possibly its larger isoforms, and intravitreal ranibizumab, a mAb antigen binding fragment that targets all VEGF isoforms and their bioactive cleavage products, received FDA approval for the treatment of neovascular AMD in 2004 and 2006, respectively (Table 1). Bevacizumab (Avastin; Genentech, Inc.), a

Table 1 Antivascular endothelial growth factor agents currently available or in development for the treatment of neovascular age-related macular degeneration

Agent	Class	Molecular target	Drug development stage	Manufacturer
Pegaptanib (Macugen)	Aptamer	$VEGF_{165}$ isoform	FDA approved	OSI/Eyetech
Ranibizumab (Lucentis)	mAb fragment	All VEGF A isoforms	FDA approved	Genentech
Bevacizumab (Avastin)	mAb	All VEGF A isoforms	Various international phase III trials	Genentech[a]
VEGF trap	Decoy receptor	All VEGF A isoforms, VEGF B, and PlGF	Phase III	Regeneron
Triamcinolone acetonide (Kenalog 40)	Corticosteroid	Antiangiogenic; specific targets unknown, possibly VEGF and others	Phase III	Bristol Myers Squibb
Bevasiranib (Cand5)	siRNA	VEGF A mRNA	Phase III	OPKO Health
AGN211745 (Sirna 027)	siRNA	VEGF R1 mRNA	Phase II	Allergan
ATG003	Topical mecamylamine	Antiangiogenic; α3β4 nicotinic Ach receptor	Phase II	CoMentis, South San Francisco, California, USA
Quark	siRNA		Phase I, II	Quark Inc., Denver, Colorado, USA; Pfizer, New York, New York, USA
JSM6427	Small molecule integrin α5β1 antagonist	Antiangiogenic; integrin α5β1	Phase I	Jerini AG, Berlin, Germany

Ach, acetylcholine; FDA, Food and Drug Administration; PlGF, placental growth factor; siRNA, small interfering RNA; VEGF, vascular endothelial growth factor; VEGF R1, vascular endothelial growth factor receptor 1.
[a] Investigations of the clinical use of bevacizumab in ocular diseases are independent of Genentech.

full length humanized mAb, was derived from the same murine anti VEGF mAb as ranibizumab. Similar to rani bizumab, bevacizumab targets all isoforms and bioactive cleavage products of VEGF A. Bevacizumab is FDA approved for use in combination with chemotherapy for the systemic treatment of metastatic colorectal, lung, and breast cancer. Systemic and intravitreal bevacizumab have also recently been used off label in neovascular AMD and other exudative eye diseases. The successful treatment of neovascular AMD with these agents as presented in the overview below serves as a proof of concept for the clinical use of anti VEGF in neovascular eye diseases.

Pegaptanib sodium

The landmark phase III VEGF Inhibition Study In Ocular Neovascularization (VISION) clinical trials showed that intravitreal pegaptanib sodium slows visual loss in neovascular AMD, with 70% of treated patients losing more than 15 letters of visual acuity compared with 55% of controls [40,41]. Moreover, 6% of pegaptanib sodium treated patients gained at least 15 letters com pared with 2% of the patients in the control group [40]. Fluorescein angiography at 30 and 54 weeks showed that the pegaptanib treated group had a significant reduction ($P < 0.01$) in the rate of growth of the total area of their CNV lesions and the severity of leakage compared with the control group [40].

Ranibizumab

The pivotal phase III Minimally Classic/Occult Trial of the Anti VEGF Antibody Ranibizumab in the treatment of Neovascular AMD (MARINA) [42] and Anti VEGF Antibody for the Treatment of Predominantly Classic CNV in AMD (ANCHOR) [43] trials established ranibi zumab as the first FDA approved agent that prevents vision loss and improves vision in a substantial proportion of patients with all subtypes of neovascular AMD. At 12 and 24 months in the MARINA trial, 90 95% of patients treated with 0.3 or 0.5 mg ranibizumab lost less than 15 letters of visual acuity compared with 53 64% of control patients; also at 12 and 24 months, 25 34% of ranibizu mab treated patients had gained at least 15 letters of visual acuity compared with 4 5% of control patients [42]. The ANCHOR trial, which compared ranibizumab with verteporfin photodynamic therapy (PDT), had similar findings at 12 and 24 months: 90 96% of the ranibizumab treated versus 64 66% of the PDT treated patients lost less than 15 letters of visual acuity, whereas 34 41% of the ranibizumab group versus 6% of the PDT group gained more than 15 letters [43] (Brown DM, personal communication).

Analyses of fluorescein angiography in both the MAR INA and ANCHOR studies also revealed statistically significant decreases in mean area and total CNV, leakage from CNV, serous sensory retinal detachment (SSRD), and disciform scar/subretinal fibrosis at both 12 and 24 months after ranibizumab treatment [43,44]. A retro spective analysis of optical coherence tomography (OCT)/fluorescein angiography prospectively collected in a subset of 46 patients from the MARINA study showed a statistically significant decrease at 12 months (final OCT) in mean foveal center point thickness of the ranibizumab treated group compared with the sham treated group [44].

Clinical studies such as Prospective OCT Imaging of Patients With Neovascular AMD Treated With Intraocular Lucentis (PrONTO) and Phase IIIb, Multi center, Randomized, Double Masked, Sham Injection Controlled Study of the Efficacy and Safety of Ranibi zumab in Patients with Subfoveal CNV with or without Classic CNV Secondary to AMD (PIER) have investi gated alternative, less frequent ranibizumab dosing strategies in an attempt to lower rates of potential treat ment related adverse events. The 2 year phase I/II open label PrONTO trial evaluated an OCT guided, variable dosing regimen of monthly intravitreal ranibizumab (0.5 mg) for 3 months followed by intravitreal ranibizu mab as needed based on OCT defined retreatment criteria in 40 patients with all subtypes of neovascular AMD [45•]. At 1 year, 95% (38/40) of treated patients had lost less than 15 letters of visual acuity; 35% (14/40) of treated patients had gained at least 15 letters of visual acuity, and the mean change in visual acuity was +9.3 letters for treated patients. The mean number of injec tions for the first year was 5.6 (range 3 13); the most common reason for reinjection was a loss of at least five letters of visual acuity in association with presence of macular fluid. The earliest signs of recurrent fluid in the macula following cessation of treatment were OCT detectable. At 12 months after treatment, the mean central retinal thickness (CRT) as measured by OCT decreased by 178 μm ($P < 0.001$). At 24 months, the results were virtually identical [a mean visual acuity change of +11.1 letters, a mean CRT/OCT decrease of 215 μm, and a mean number of injections of 10 (range 3 25) over 2 years] (Rosenfeld PJ, personal communi cation). The PrONTO trial showed that in future clinical trials it may be possible to use qualitative OCT to determine the basis for retreatment.

The 2 year PIER trial [46•] examined the efficacy and safety of 0.3 or 0.5 mg ranibizumab monthly for 3 months followed by quarterly dosing. The first year data showed that a significantly greater proportion of patients receiv ing ranibizumab lost less than 15 letters of visual acuity (83.3% of patients in the 0.3 mg group and 90.2% of patients in the 0.5 mg group) compared with 49.2% of patients in the sham treatment group ($P < 0.0001$ for each dose level versus sham). However, there was no signifi cant difference in the proportion of patients who gained at least 15 letters: 11.7 and 13.1% of treated patients (0.3 and 0.5 mg, respectively) compared with 9.5% in the sham group. Although the overall safety profile of ranibizumab in the PIER trial was similar to the first year of the MARINA and ANCHOR trials, the efficacy outcomes of the PIER trial were less beneficial than the MARINA and ANCHOR trials because some patients required more frequent dosing than quarterly dosing to achieve maximal benefit. On the basis of the PrONTO and PIER trials, OCT guided administration of less frequent ranibizumab retreatment appears to be beneficial.

The recently completed Safety Assessment of Intra vitreal Lucentis for AMD (SAILOR) trial was a single masked, multicenter phase IIIb study to evaluate the safety and tolerability of two doses of intravitreal rani bizumab in patients with neovascular AMD. Safety assessments showed higher stroke rates with increased dosage (0.7 and 1.2% for the 0.3 and 0.5 mg groups, respectively), but the difference was not statistically significant [47••]. Prior stroke was the most significant risk factor for stroke. Frequencies of cardiovascular events and ocular serious AEs were similar for the two dose groups [47••,48]. A subgroup analysis of this study showed an association between greater improve ments in visual acuity and central foveal thickness in patients presenting with a higher baseline visual acuity [49].

Intravitreal bevacizumab

Although systemic bevacizumab (5 mg/kg) has been shown to reduce leakage from CNV, decrease CRT, and significantly improve vision in neovascular AMD [50 52], intravitreal administration is perceived to be safer and requires less frequent retreatment [50,51]. In the first reported case study [53] of intravitreal bevaci zumab, a patient with recurrent CNV secondary to AMD, who had previously been treated with pegaptanib and with PDT in combination with triamcinolone acetonide, experienced resolution of visual distortion within 1 week in parallel with resolution of subretinal fluid and a reduction in CRT following a single injection of 1.0 mg bevacizumab. Subsequently, several retrospec tive [54 67] and prospective [68 79] studies of intra vitreal bevacizumab (dose range 1.0 2.5 mg) in neovascular AMD have been published, invariably demonstrating clinically significant improvement in mean visual acuity, reduction in fluorescein angiography leakage and CRT, and resolution of edema in up to 90% of bevacizumab treated patients. Most studies were small (up to 100 patients) uncontrolled studies with different retreatment criteria and outcome measures. Systemic and ocular AEs were rare; the most common ocular side effects were endophthalmitis, uveitis, sub macular hemorrhage, and RPE tears. In a recent retro spective safety assessment of intravitreal bevacizumab involving 1173 patients, 18 (1.5%) reported systemic AEs, including five (0.4%) deaths, whereas ocular AEs included subconjunctival hemorrhage [838 cases (19% of 4303 injections)] and increased intraocular pressure (IOP), endophthalmitis, and tractional retinal detach ment [seven cases (0.16%) each] [67]. The low rates of systemic complications in these studies were consistent with those reported in an earlier survey of 5228 patients [80].

A randomized, prospective clinical trial compared verteporfin PDT with bevacizumab (2.5 mg) for the treatment of predominantly classic CNV secondary to AMD and found that at month 6, all 32 eyes (100%) receiving bevacizumab lost 15 letters or less in visual acuity compared with 73.3% of the PDT receiving eyes ($P = 0.002$) [76]. Mean CRT was significantly better at 3 and 6 months in patients treated with bevacizumab versus the PDT group ($P = 0.04$ and $P = 0.002$, respectively). The study showed overall benefit of treatment with bevacizumab compared with PDT.

Combination therapy

Small short term studies evaluating the combination of intravitreal bevacizumab with PDT versus PDT alone [81–83] and bevacizumab as well as pegaptanib sodium [84] for neovascular AMD have demonstrated clinical benefits (visual acuity improvement and resolution of edema), suggesting possible synergistic effects. However, these findings require confirmation in large randomized controlled trials. Currently, combinations of two or three therapies, compared with anti VEGF monotherapy, are being tested for their ability to reduce the intervention rate with equivalent efficacy and safety outcomes. These include the combination of ranibizumab as well as PDT, bevacizumab monotherapy versus bevacizumab as well as PDT, or bevacizumab as well as PDT and triamcinolone, and bevacizumab as well as triamcinolone.

An ongoing phase I trial (http://www.clinicaltrials.gov, NCT00569140) is evaluating the safety, tolerability, and pharmacokinetic profile of intravitreal E10030 (Ophthotech Corporation, Princeton, New Jersey, USA) in patients with neovascular AMD receiving ranibizumab or bevacizumab. E10030 is a pegylated aptamer that targets platelet derived growth factor (PDGF). The rationale for the study is that PDGF and VEGF have independent angiogenic activities, and preclinical studies have demonstrated that the combination of E10030 and anti VEGF agents has more potent antiangiogenic results than anti VEGF treatment alone (Ophthotech Corporation press release, 12 February 2008).

Sorafenib (Nexavar; Bayer HealthCare Pharmaceuticals, Wayne, New Jersey, USA) is a tyrosine kinase inhibitor that diminishes VEGF signaling by inhibiting VEGFR and has been approved for the treatment of certain cancers. Recently, a report described two neovascular AMD patients who received off label oral sorafenib (200 mg three times per week) in combination with ongoing intravitreal ranibizumab treatment in an attempt to decrease the number of ranibizumab injections [85]. Both patients experienced stable or improved visual acuity and improvement in CRT after initiation of sorafenib therapy. Therefore, it will be of interest to evaluate the effects of sorafenib in combination with ranibizumab or as monotherapy in larger patient cohorts, especially in patients with refractory or recurrent neovascular AMD.

The safety and efficacy of a unique combination therapy consisting of focal strontium 90 beta radiation delivered via the Epi Rad90 Ophthalmic System (NeoVista, Fremont, California, USA) as well as ranibizumab, versus ranibizumab alone, is being evaluated in neovascular AMD in the ongoing randomized, open label, active control phase III CNV secondary to AMD treated with Beta Radition Epiretinal Therapy (CABERNET) trial (http://www.clinicaltrials.gov; NCT00454389).

Other strategies to inhibit vascular endothelial growth factor signal transduction

Several different anti VEGF and antiangiogenic agents have demonstrated efficacy in neovascular AMD. A phase II randomized, double masked trial of VEGF trap (Regeneron Pharmaceuticals, Tarrytown, New Jersey, USA), a fusion protein of VEGF receptor ligand binding domains and the immunoglobulin G type 1 (IgG1) Fc region, demonstrated increases in visual acuity from baseline of 9.0 letters ($P < 0.0001$) and 5.4 letters ($P < 0.085$) at 52 weeks after fixed monthly or quarterly dosing (0.5, 2, or 4 mg) for 12 weeks followed by another 40 weeks on an as needed basis in neovascular AMD (AZ Regeneron press release, 28 September 2008). Patients receiving monthly VEGF trap (2.0 or 0.5 mg for the first 12 weeks) also experienced mean reductions in CRT of 143 and 125 μm, respectively, at week 52 ($P < 0.0001$ for both from baseline). Currently, two randomized, international phase III studies (VIEW 1 and VIEW 2) (http://www.clinicaltrials.gov; NCT00509795, NCT00637377) are comparing intravitreal VEGF trap with ranibizumab.

Small interfering RNA (siRNA) agents designed to silence the *VEGF* gene and the VEGFR have been shown in preclinical studies to inhibit ocular neovascularization and vascular permeability in animal models [86,87]. Bevasiranib (previously called Cand5; OPKO Health, Inc./Acuity Pharmaceuticals, Miami, Florida, USA) and AGN211745 (previously called Sirna 027; Allergan, Inc., Irvine, California, USA) are currently being studied in phase II and III clinical trials, respectively, in neovascular AMD. In a phase II randomized trial, bevasiranib (single intravitreal injections at baseline and week 6) was shown to be well tolerated after 12 weeks of follow up, with mild AEs related primarily to the injection procedure and with no systemic exposure. Bevasiranib stabilized visual acuity in most patients and improved visual acuity in more than one third of patients (Acuity Pharmaceuticals press release, 11 September 2006). The Combining Bevasiranib and Lucentis (ranibizumab)

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