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# Neovascular Age-Related Macular Degeneration

## Potential Therapies

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## Abstract

Age-related macular degeneration (AMD) affects an estimated 14 million people worldwide, and is the leading cause of severe, irreversible vision loss in individuals over the age of 50 years in Western societies. Choroidal neovascularization (CNV), the hallmark of 'wet', 'exudative' or 'neovascular' AMD, is responsible for approximately 90% of cases of severe vision loss due to AMD. Vascular endothelial growth factor (VEGF) has been shown to play a key role in the regulation of CNV and vascular permeability. Ranibizumab, the current gold standard in the US for the treatment of neovascular AMD, exerts its effect through binding and inhibition of all isoforms of VEGF. Randomized controlled clinical trials have established ranibizumab as the first US FDA-approved therapy for neovascular AMD to result in improvement in visual acuity. Despite impressive outcomes, treatment with ranibizumab requires sustained treatment regimens and frequent intravitreal injections. In this review, we discuss promising emerging therapies for neovascular AMD that aim to improve outcomes, safety and treatment burden through novel mechanisms of action. Currently in phase III clinical trials, VEGF Trap is a receptor decoy that targets VEGF with higher affinity than ranibizumab and other currently available anti-VEGF agents. Another promising therapeutic strategy is the blockade of VEGF effects by inhibition of the tyrosine kinase cascade downstream from the VEGF receptor; such therapies currently in development include vatalanib, TG100801, pazopanib, AG013958 and AL39324. Small interfering RNA technology-based therapies have been designed to downregulate the production of VEGF (bevasiranib) or VEGF receptors (AGN211745) by degradation of specific messenger RNA. Other potential therapies include pigment epithelium-derived factor-based therapies, nicotinic acetylcholine receptor antagonists, integrin antagonists and sirolimus.

Age-related macular degeneration (AMD) is the leading cause of severe, irreversible vision loss in individuals over the age of 50 years in Western societies. AMD affects an estimated 14 million people worldwide,[1] and the number of individuals in the US with AMD is estimated to increase from 1.75 million in 2000 to 2.95 million in 2020.[2] Choroidal neovascularization (CNV) is the hallmark of 'wet', 'exudative' or 'neovascular' AMD, and is responsible for approximately 90% of cases of severe vision loss due to AMD.[3] The magnitude of this burden on society has driven research efforts aimed at the prevention and treatment of vision loss due to AMD. Until the introduction of photodynam-

ic therapy (PDT) with verteporfin in 2000, laser photocoagulation as described in the MPS (Macular Photocoagulation Study)[4] had been the mainstay of treatment for subfoveal CNV. Visual acuity outcomes improved with PDT, but patients continued to experience a decline in visual acuity (mean loss of 1.6 lines at 60 months).[5] Pegaptanib was the first AMD therapy to selectively block vascular endothelial growth factor (VEGF), a key proangiogenic factor. Pegaptanib was well tolerated,[6] but failed to offer a distinct advantage in visual outcome over PDT, possibly because of it selectively binds only to VEGF165.

Both bevacizumab and ranibizumab bind and inhibit all isoforms of VEGF-A. There are subtle but important differences between these two molecules. Bevacizumab is the humanized version of a mouse monoclonal antibody to VEGF-A and is made in a Chinese hamster ovary expression system that glycosylates the protein. In contrast, ranibizumab is a humanized version of the Fab fragment of the same mouse monoclonal antibody to VEGF-A that has been affinity matured to provide approximately 10-fold greater VEGF binding than bevacizumab. It is produced in an *Escherichia coli* expression system that does not glycosylate the protein. Ranibizumab was the first therapy for neovascular AMD to result in significant improvement in visual acuity in all lesion subtypes[7,8] of neovascular AMD. Intravenous bevacizumab is US FDA approved for the treatment of metastatic colorectal cancer, but has been used off-label by both intravenous and intravitreal routes for the treatment of CNV. There have been numerous small case series that have shown the efficacy of bevacizumab therapy for CNV. Beyond the differences in the molecules, a ranibizumab treatment costs approximately $US2000 per dose, whereas a bevacizumab treatment for AMD costs approximately $US50–100 (2007-8 costings). It is not known if ranibizumab and bevacizumab have similar efficacy and safety. The National Eye Institute's CATT (Comparison of Age-Related Macular Degeneration Treatment Trials) will compare bevacizumab and ranibizumab head-to-head. Currently in the planning stages, the study hopes to randomize 1200 participants with subfoveal CNV secondary to AMD to bevacizumab or ranibizumab (either in a fixed or variable dose administration schedule) in a total of four treatment groups.[9] Until the results of this study are known, the gold standard in the US for the treatment of neovascular AMD is ranibizumab. However, despite the impressive visual gains of this treatment, there is room for improvement in outcomes and safety.

In this review, we discuss novel antiangiogenic therapies for neovascular AMD that show promise and are currently in clinical development (figure 1). Because of the very recent nature of the data reported in this manuscript, many of the references cited have not had the benefit of peer review, and are culled from abstracts and presentations at major scientific meetings. Therefore, the reader should interpret such data with appropriate discretion until more rigorous clinical testing of these compounds has been completed.

## 1. Vascular Endothelial Growth Factor (VEGF)

The VEGF family comprises VEGF-A (often referred to simply as VEGF), VEGF-B, VEGF-C, VEGF-D and placental growth factor (PlGF)-1 and -2. VEGF gene expression is primarily regulated by hypoxia, growth factors and nitric oxide, and its effect is exerted through at least three different receptors located on vascular endothelial cells. VEGF has been shown to play a key role in regulation of retinal neovascularization and CNV, and impart increased vascular permeability. VEGF expression has been implicated in the development of neovascularization in diabetic retinopathy, retinal vein occlusion, iris neovascularization, retinopathy of prematurity and neovascular AMD. Because of its central role in the development of CNV in AMD, it is an attractive target for potential therapies.

### 1.1 VEGF Trap

VEGF Trap is a receptor decoy with a higher affinity for VEGF than native VEGF receptors or any of the currently available anti-VEGF drugs. VEGF Trap is a recombinant protein composed of

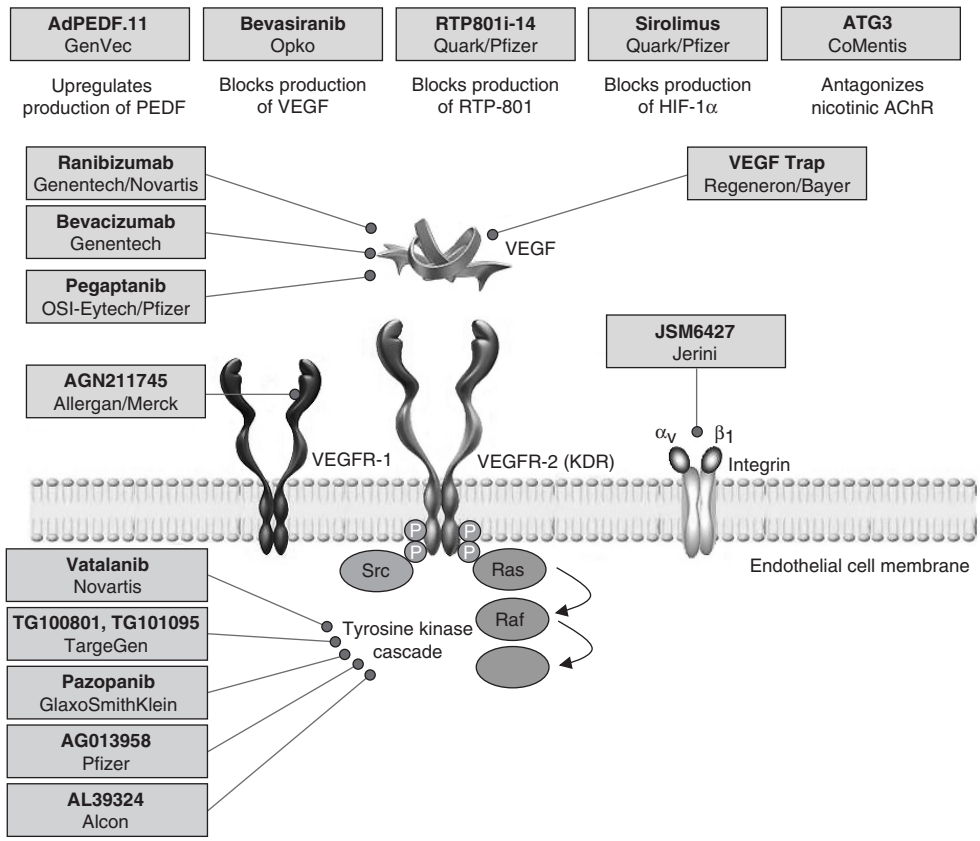


**Fig. 1.** Summary of currently available treatments and novel antiangiogenic therapies that are in development for neovascular age-related macular degeneration, including manufacturer and indicating target of action. **AChR** = acetylcholine receptor; **HIF-1α** = hypoxia-inducible factor-1α; **PEDF** = pigment epithelium-derived factor; **RTP-801** = hypoxia-inducible gene; **VEGF** = vascular endothelial growth factor; **VEGFR** = vascular endothelial growth factor receptor.

key ligand-binding domains from VEGF receptor (VEGFR)-1 and -2 combined with the Fc portion of human $IgG_1$. Unlike pegaptanib, ranibizumab and bevacizumab, which all act through inhibition of VEGF-A, VEGF Trap is designed to inhibit all members of the VEGF family: VEGF-A, -B, -C, -D and PlGF-1 and -2.

Data from a phase I, randomized, double-blind, placebo-controlled, ascending-dose trial of 25 patients with AMD showed a dose-dependent decrease in retinal thickness in patients who received intravenous VEGF Trap.[10] However, dose-limiting toxicity (hypertension in one patient and proteinuria in another patient) was observed,[10] and the study and further clinical development of systemic VEGF Trap for ocular disease was halted.

The safety, tolerability and bioactivity of intravitreal VEGF Trap for the treatment of neovascular AMD was evaluated in the two-part CLEAR-IT-1 (Clinical Evaluation of Anti-angiogenesis in the Retina Study).[11] In part 1, 21 patients were randomized to receive one of six doses of VEGF Trap (0.05, 0.15, 0.5, 1, 2 or 4 mg) as a single intravitreal injection at baseline, then assessed at 1, 2, 4 and 6 weeks using ETDRS (Early Treatment Diabetic Retinopathy Study) best-corrected visual acuity (BCVA), fluorescein angiography and optical coherence tomography (OCT). VEGF Trap was well tolerated and the maximum tolerated dose was not

reached; furthermore, no adverse ocular or systemic events were observed. At 6 weeks, visual acuity remained stable or improved in 95% of patients[12] and the total area of active CNV leakage decreased by a median of 33.7% ($p = 0.001$).[11] Part 2 was a randomized, dose-ranging study in which 24 subjects received a single dose of either 0.15 or 0.4 mg VEGF Trap, with a final study endpoint at 8 weeks. Both groups showed decreases in the greatest height of subretinal fluid and pigment epithelial detachment, with the maximal effect observed at 2 weeks. A significant difference between the treatment groups in central retinal thickness was noted at 8 weeks.[13]

Interim analysis on the first 78 patients who completed 12 weeks of the CLEAR-IT-2 study (phase II, randomized, controlled, clinical trial of 125 patients to receive one of five treatment regimens: 0.5 mg or 2.0 mg every 4 weeks, or 0.5 mg, 2.0 mg or 4.0 mg every 12 weeks) demonstrated that with all groups combined, VEGF Trap met its primary endpoint of a statistically significant mean reduction in central retinal thickness on OCT.[14] Mean change from baseline in visual acuity in all patients showed a statistically significant improvement (increase of 5.9 letters) in vision. Monthly (vs quarterly) dose administration showed a trend towards greater improvement in BCVA at 12 weeks, although this difference was not statistically significant and is being studied in greater detail in the extension study.[14] A long-term, phase II, safety and efficacy study for subjects previously enrolled in phase I and II studies is currently ongoing, with 3-year follow-up and September 2010 completion anticipated.[15] VEGF Trap is currently in a large phase III trial, which is a head-to-head, non-inferiority trial versus ranibizumab.

## 2. Tyrosine Kinase Inhibitors

Another method of inhibiting the effects of VEGF is through inhibition of the downstream tyrosine kinase cascade activated when VEGF attaches to its receptors (figure 1). Vatalanib (formerly PTK/ZK) is a multi-VEGF receptor inhibitor that binds to the intracellular kinase domain of all three VEGF receptors (VEGFR-1, -2 and -3). Intravitreal injection of vatalanib has been shown to reduce angioproliferative changes in a mouse model of ischaemic-induced retinopathy.[16] A phase I/II study of daily systemic vatalanib given orally in conjunction with either PDT (vs PDT alone) or ranibizumab (vs ranibizumab alone) for subfoveal CNV is currently underway, with no results publicly reported to date.[17] Vatalanib has a high oral bioavailability and, therefore, the use of adjunctive vatalanib may present an attractive alternative to the use of currently available intravitreally administered agents.

Other tyrosine kinase inhibitors currently in development include the topical formulations pazopanib, TG100801 and TG101095, a subtenon formulation AG013958, and an intravitreal formulation AL39324 (see figure 1). A phase II study of oral pazopanib for renal cell carcinoma is currently ongoing, and the safety of pazopanib as a topical therapy for neovascular AMD is being evaluated in a randomized, placebo-controlled, dose-escalation study that began enrolment in March 2007.[18] TG101095 specifically targets tyrosine kinases associated with VEGFR-2 and is another candidate for topical administration. Twice daily application of 1% TG101095 has been shown to reduce CNV in the murine laser-induced model; furthermore, microscopic and histopathological examination of treated eyes indicated it is well tolerated.[19] In a phase I trial completed in February 2007, TG100801 was well tolerated by 42 healthy volunteers when administered topically twice daily for 14 consecutive days.[20] A phase IIa pilot study of TG100801 in patients with neovascular AMD commenced in July 2007. Finally, in preclinical studies, AL-39324 has been shown to dose-dependently block VEGF-induced increases in bovine retinal endothelial cells *in vitro* and reduce CNV lesion size in the murine laser-induced CNV model.[21]

## 3. Pigment Epithelium-Derived Factor

Whereas the presence of VEGF in the eye promotes new blood vessel growth and leakage, pigment epithelium-derived factor (PEDF) is a potent antiangiogenic factor. Delivery of an adenoviral

vector carrying complimentary DNA encoding human PEDF, AdPEDF.11, to the vitreous or subretinal space has been shown to induce regression of ocular neovascularization in two animal models.[22] These preclinical data have recently been supplemented by phase I clinical trial results that found no serious adverse events or dose-limiting toxicity in patients with neovascular AMD.[23] Although this trial was not designed to evaluate efficacy, the data suggested antiangiogenic activity persisting for several months following a single intravitreal dose of at least $10^8$ particle units. Therapy does not appear to initiate a systemic immune response; thus, the possibility of repeat injections exists.

### 4. Nicotinic Acetylcholine Receptor Antagonists

The recent description of an endogenous cholinergic pathway for angiogenesis[24] opens the door for yet another avenue for therapeutic inhibition of ocular angiogenesis. Both pharmacological inhibition of nicotinic acetylcholine receptor (nAChR) and genetic disruption of nAChR expression have been shown to significantly reduce ischaemia-induced angiogenesis *in vivo*.[24] ATG3, an ophthalmic formulation of the nAChR antagonist mecamylamine, reduced CNV lesion size when administered intravitreally in a murine laser-induced model of CNV.[25] Furthermore, ATG3 showed good ocular tolerability and lack of serious adverse effects in a randomized, double-blind, placebo-controlled, phase I study of 80 healthy volunteers.[26] A 330-patient, placebo-controlled, phase II, clinical trial of patients with neovascular AMD is currently enrolling and aims to assess the safety and efficacy of twice daily administration of two different doses of ATG3 for up to 48 weeks.[26] Interim (6-month) efficacy data is expected by mid-2008.

### 5. Small Interfering RNA

Small interfering RNA (siRNA)-based therapies silence production of specific genes and, thus, their protein products by activation of an innate cellular defence mechanism. Double-stranded RNA (dsRNA) is recognized by a cell as evidence of possible infection by an RNA virus. When an RNA virus enters or synthetic dsRNA is injected into the cell, the enzyme Dicer processes it into nucleotide sequences – siRNA. The siRNA then binds to an RNA-induced silencing complex (RISC). This activated complex, in turn, targets and degrades complementary messenger RNA (mRNA). One activated RISC complex is capable of binding and destroying hundreds of complementary mRNA, which, in turn, prevents the formation of thousands of protein copies, thus making this a very potent process. Although any dsRNA can be processed into siRNA, the introduction of dsRNA into a cell can trigger another endogenous antiviral defence, the interferon response. Thus, introduction of manufactured siRNA is a more viable therapeutic option.

siRNA technology works by downregulating the production of certain proteins by degradation of specific mRNA. In neovascular AMD, two protein targets for siRNA technology include VEGF and a VEGFR. Unlike existing anti-VEGF therapies, siRNA would prevent the formation of VEGF or VEGFRs. Clinically, the use of intravitreal RNA-based molecules has shown minimal toxicity.[27] Several promising therapeutic agents have emerged that use siRNA technology against VEGF and VEGFRs.

Bevasiranib (formerly Cand5) is an siRNA that targets VEGF-A mRNA, and has been shown to reduce the amount of VEGF-A produced under hypoxic conditions *in vitro* and *in vivo*.[28] In a murine laser-induced model of CNV, bevasiranib significantly reduced the size of CNV.[28] The CARE (Cand5 Anti-VEGF RNAi Evaluation) study is a phase II, randomized, double-blinded trial designed to assess the safety and efficacy of bevasiranib in 129 patients with CNV secondary to AMD.[27] Patients with predominantly classic or minimally classic lesions were randomized to receive one of three doses of bevasiranib (0.2, 1.5 or 3.0 mg) at baseline and at 6 weeks. Patients were examined, and OCT and fluorescein angiography obtained every 3 weeks for 18 weeks. No serious adverse events or dose-limiting toxicities were observed.[27] However, bevasiranib-treated patients performed only margin-

ally better on ETDRS visual acuity than would be expected for natural history based on TAP (Treatment of Age-related macular degeneration with Photodynamic therapy) study data, with all three dosage groups losing mean visual acuity over 18 weeks. Lesion size also increased on fluorescein angiography in all three groups at 12 weeks.[27] Because the action of bevasiranib is to block the production of VEGF, VEGF in the eye at the time of administration precludes immediate impact of the anti-VEGF activity of the drug. Thus, concomitant administration of a therapeutic agent that binds VEGF protein may enhance the efficacy of bevasiranib. Currently in enrolment, the phase III COBALT (Combining Bevasiranib And Lucentis® [1] [ranibizumab] Therapy) investigation will assess the safety and efficacy of bevasiranib administered every 8 weeks or 12 weeks as maintenance therapy following 3 monthly injections of ranibizumab (vs ranibizumab monotherapy monthly) in 330 patients with neovascular AMD.[29]

Another product that uses siRNA technology is AGN211745 (formerly SIRNA-027), which targets the mRNA for VEGFR-1. A 57% reduction in VEGFR-1 mRNA was demonstrated after single intravitreal injection of AGN211745 in mice.[30] In addition, intravitreal injection in a murine laser-induced model of CNV resulted in 45% reduction in area of neovascularization.[30] A phase I, dose-escalation trial in 26 patients with neovascular AMD found that a single intravitreal dose of AGN211745 to be safe and well tolerated.[15] Visual acuity stabilization at 3 months was achieved in 92% of patients, and decreased foveal thickness consistent with biological activity was observed in some patients. A phase II, 24-month, single-blinded, parallel assignment, safety/efficacy study is currently in enrolment.[31]

RTP801i-14 is a siRNA drug candidate that inhibits the expression of hypoxia-inducible gene RTP801, which promotes the generation of reactive oxygen species *in vitro*, probably through a VEGF-independent mechanism. Inhibition of RPT801 expression in genetic (RTP801-knockout) and therapeutic (intravitreal RTP801i-14 injection) models of laser-induced CNV has been shown to inhibit or reduce CNV formation and vessel leakage.[32] RTP801i-14 is currently in phase I/IIa testing.

## 6. Sirolimus

Although sirolimus was approved by the FDA for prevention of transplant rejection in 1999 and for use in drug-eluting coronary stents in 2003, it is currently in phase I clinical trials for use in ophthalmic applications. Sirolimus, also known as rapamycin, targets the protein kinase mammalian target of rapamycin, which regulates cell growth and metabolism. In addition to possessing anti-inflammatory, anti-fibrotic and anti-proliferative properties, sirolimus acts as an antiangiogenic agent by decreasing VEGF and transforming growth factor-β1.[33] Sirolimus also exerts an antiangiogenic effect through a second mechanism: downregulation of hypoxia-inducible factor-1α, which effectively decreases VEGF production and inhibits VEGF-induced endothelial cell proliferation. Because sirolimus is a small, highly lipophilic molecule, it is an excellent candidate for sustained ocular delivery.

In preclinical studies, sirolimus inhibited VEGF-induced hyperpermeability in mice[34] and reduced CNV in a murine laser-induced model of CNV.[35] An ongoing, phase I, randomized, dose-escalation study aims to investigate the safety and tolerability of a proprietary formulation of sirolimus via single-dose, subconjunctival or intravitreal injection.[36] Retinal thickness, as assessed by OCT, at 45 days and 90 days after injection may provide preliminary data on efficacy. A randomized, phase II trial of 20 patients with neovascular AMD currently in enrolment will assess the efficacy of systemic sirolimus (given as a pill every other day) or one of two other immunomodulatory agents (infliximab or daclizumab) in conjunction with continued antiangiogenic therapy.[37] CNV lesion size, as assessed by fluorescein angiogram, will be the primary outcome measure; BCVA and retinal thickness on OCT will serve as secondary outcome measures.

**1** The use of trade names is for product identification purposes only and does not imply endorsement.

## 7. Integrin Antagonists

Integrins are cell surface receptors that mediate survival signals from the extracellular matrix. Certain subpopulations of integrins ($\alpha_v\beta_3$, $\alpha_v\beta_5$ and $\alpha_v\beta_1$) show increased expression on vascular endothelial cells participating in retinal neovascularization. However, of these, only $\alpha_v\beta_1$ has been shown to also be upregulated in vascular cells in an animal model of CNV.[38] Preclinical studies of a selective $\alpha_v\beta_1$ antagonist, JSM6427, aim to either induce regression[38] or dose-dependently prevent development[39] of CNV in animal models. The safety and tolerability of JSM6427 will be evaluated in a phase I clinical trial, which began recruitment in October 2007.

## 8. Conclusion

Currently available therapies that work through nonselective VEGF blockade have, for the first time, afforded patients with neovascular AMD the possibility of regaining vision. However, the effects are short lived and sustained treatment regimens involving frequent intravitreal injections are required. As we come to better understand the multifactorial nature of ocular angiogenesis in AMD, we are able to develop therapies that target many different aspects of the angiogenesis cascade. The use of such therapies in combination with currently available anti-VEGF agents holds promise for the provision of rapid and sustained improvement in vision with minimal treatment burden.

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