Bevacizumab for Ophthalmic Disease

a report by
Lucienne Collet, MD, Theresa A Larson, MD *and* **Sophie J Bakri, MD**

Department of Ophthalmology, Mayo Clinic *DOI: 10.17925/USOR.2007.02.00.20*

The introduction of anti-angiogenic agents has revolutionized the treatment of vascular endothelial growth factor (VEGF)-mediated ocular disease. The first anti-angiogenic agent to be approved by the US Food and Drug Administration (FDA), bevacizumab, was originally developed to inhibit tumorigenesis. It has found widespread application in the treatment of ophthalmic disease, the pathophysiology of which involves neovascularization. Bevacizumab is used off-label intravitreally to treat ocular diseases with high VEGF levels, such as choroidal neovascularization (CNV), proliferative diabetic retinopathy, diabetic maculopathy, and retinal vein occlusion. In some cases it is used intravenously.

In the last 10 years, intensive research on activators and inhibitors of angiogenesis (the process whereby new blood vessels are formed from pre-existing vessels) has increased our knowledge of neovascular ocular pathology. Various angiogenic factors that stimulate the growth of new vessels and increase vascular permeability have been identified, and a few have been found to be responsible for neovascularization in the eye.[1,2] VEGF, also known as VEGF-A or vascular permeability factor (VPF),[3] was first identified in 1989 by Napoleone Ferrara, who purified VEGF from conditioned media of bovine pituitary follicular.[4] Further characterization resulted in the discovery of four active human isoforms of VEGF consisting of 121, 165, 189, and 206 amino acids. Numerous effects on endothelial cells were found when VEGF was inhibited—without VEGF, endothelial cells in immature vessels could not survive, and endothelial cells were unable to grow and proliferate.[5]

Sophie J Bakri, MD, is Assistant Professor of Ophthalmology at the Mayo Clinic, Rochester, Minnesota. Her special interests are diseases and surgery of the retina and vitreous, in particular diabetic retinopathy, age-related macular degeneration (AMD), intravitreal anti-vascular endothelial growth factor (VEGF) agents, and the repair of complex retinal detachments. She undertakes both clinical and translational research in drugs for choroidal neovascularization (CNV) and other VEGF-mediated diseases. Dr Bakri is board-certified by the American Board of Ophthalmology (ABO). She has authored more than 40 peer-reviewed papers and 12 book chapters on retinal diseases, is an investigator for numerous multicenter clinical trials on new medications for retinal disease, and is Editor-in-Chief of the book *Mayo Clinic on Vision and Eye Health*. She has been an invited reviewer for many journals, including *Ophthalmology*, *Archives of Ophthalmology*, the *American Journal of Ophthalmology*, the *British Journal of Ophthalmology*, and *Retina*. Dr Bakri has presented her work and been an invited speaker at national and international meetings on numerous occasions. She completed a two-year vitreoretinal fellowship at the Cleveland Clinic Foundation, Cleveland, Ohio, before completing her residency at the Albany Medical College, New York, where she was elected Chief Resident. She graduated from the Queen's Medical Center, University of Nottingham Medical School, England, where she obtained her degree in medicine and surgery and her bachelor of medical sciences.

E: sbakri@hotmail.com

In subsequent years, evidence accumulated in both clinical and animal studies as to the pivotal role of VEGF in ocular neovascularization. Increased vitreous VEGF levels were found in diabetic retinopathy, diabetic maculopathy, and retinal vein occlusion.[6] This led to the development of a therapeutic armamentarium targeted at selective inhibition of VEGF with antibodies, fragments of antibodies, and aptamers. The first agents designed for ocular use, pegaptanib (an RNA aptamer) and ranibizumab (an antibody fragment to all isoforms of VEGF), demonstrated success in clinical trials for neovascular age-related macular degeneration (AMD). In 2004, with the FDA approval of bevacizumab for metastatic colorectal cancer and the awaited approval of ranibizumab, bevacizumab was used off-label for neovascular AMD.

Bevacizumab

Bevacizumab is a 150kD full-length recombinant humanized monoclonal antibody that binds to all isoforms of VEGF.[7] It is approved by the FDA for systemic treatment of metastatic colorectal cancer, and is first-line treatment for recurrent or metastatic non-small-cell lung cancer. It is a humanized monoclonal immunoglobulin-G antibody that is 93% human and 7% murine in protein sequence.[8] The humanization decreases the risk for an immunological response and increases its half-life. It is produced through recombinant biotechnology from a Chinese hamster ovary cell line.[9] Bevacizumab prevents VEGF from binding to its receptors and subsequently inhibits receptor signaling pathways.[10] Additionally, it has been observed that it inhibits the growth of various tumor cell lines and animal tumor models,[11] such as breast and lung cancer,[12] by blocking tumor angiogenesis. Interestingly, studies using magnetic resonance imaging (MRI) showed decreased microvascular permeability as early as 24 hours after anti-VEGF treatment.[13] Early pre-clinical data on bevacizumab were obtained from oncological studies, as it was originally designed for cancer treatment.

Pharmacokinetic Properties

Pre-clinical studies on pharmacokinetics of intravenous bevacizumab show that serum half-life is one to two weeks,[11] and clinical studies in patients with advanced cancer show a half-life 21 days.[14] In a rabbit pharmacokinetic model, a dose of 1.25mg of intravitreal bevacizumab has a half-life of 4.32 days[15] and concentrations greater than 10µg/ml lasted in the vitreous for 30 days. In the aqueous humor, bevacizumab peak concentration was 37.7µg/ml three days after its administration. Eight days after intravitreal administration a maximum serum concentration of 3.3µg/ml was achieved. Interestingly, very low concentrations of bevacizumab were detected in the vitreous as well as in the aqueous humor of the contralateral uninjected eye. In vitrectomized eyes, the half-

life of an intravitreal injection of 1.25mg of bevacizumab is approximately three days, and complete VEGF blockade is achieved for four weeks.[16]

Ophthalmic Use

The first prospective study using intravenous bevacizumab for exudative AMD was the Systemic Avastin for Neovascular AMD (SANA) study. It demonstrated vision improvement of two to three lines at three months. The only significant adverse event reported was an increase in blood pressure.[17,18] The patients were treated with systemic infusions of 5mg/kg given at two-week intervals, and re-treatment was given if there was an increase in retinal thickness or macular fluid on optical coherence tomography (OCT). After an observation period of three months, the mean visual acuity improved from 20/80 to 20/50, and central retinal thickness decreased from a mean of 417 to 240µm. Researchers in Europe compared a lower systemic dose of bevacizumab of 2.5mg/kg with the typical oncological dose of 5mg/kg. There were no differences between treatment groups at six months, and results were comparable to the SANA study at six months.[19] The differences between systemic versus intravitreal bevacizumab were found not to be significant when comparing a systemic dose of 5mg/kg with an intravitreal dose of 1mg in patients with exudative AMD at three months.[20] Systemic bevacizumab has the potential risk for thromboembolic events. The advantages of systemic bevacizumab are the prolonged duration of its effect compared with intravitreal injection, and simultaneous treatment of both eyes if the condition is bilateral.

> In 2004, with the US Food and Drug Administration approval of bevacizumab for metastatic colorectal cancer and the awaited approval of ranibizumab, bevacizumab was used off-label for neovascular age-related macular degeneration.

Initially, there was controversy concerning whether intravitreal bevacizumab, as a large full-length antibody, could penetrate the retina, until various reports confirmed full retinal penetration after intravitreal injection.[21,22] Furthermore, experimental animal studies observed no evidence of retinal toxicity at maximum doses of 5mg per intravitreal injection.[23–25] Electroretinography (ERG) studies confirmed histological findings that show no differences in the recordings in bevacizumab-treated eyes compared with control eyes.[23,25] Additionally, no evidence of a toxic effect was observed in patients treated with 1.25mg of bevacizumab for exudative AMD measured by full-field and multifocal ERG.[26]

Intravitreal bevacizumab for the treatment of exudative AMD was first reported in 2005.[27] Since then it has gained widespread acceptance due to its short-term effectiveness, safety profile, worldwide availability, and its inexpensiveness compared with other anti-angiogenic drugs for intraocular use. Publications regarding intravitreal bevacizumab for the treatment of exudative AMD include six prospective studies,[28–33] one uncontrolled randomized trial,[9,34] retrospective studies,[35–43] and uncontrolled case series. The majority of the papers showed mean improvement in visual acuity and a reduction in macular thickness after intravitreal injection of bevacizumab. As yet there are no phase III clinical trials evaluating bevacizumab in AMD.

Drug Preparation, Dosage, and Administration

Bevacizumab is supplied as 25mg/ml in two vials of different sizes—100mg/4ml or 400mg/16ml of sterile concentrate solution for infusion. The excipients are polysorbate, sodium phosphate, trehalose dehydrate, and water for injection. The vial is partitioned by compounding pharmacies into several smaller doses using sterile technique, and the syringes are stored at 4°C. Dextrose 5% is not recommended for further dilution based on documented physico-chemical incompatibility. The anti-angiogenic activity was studied after refrigeration: bevacizumab was degraded by 1.6% at one week, 0% at three weeks, 8.8% at three months, and 15.9% at six months. When frozen at -10°C it was degraded by 12% at six months.[44]

Indications for Use in Ophthalmology

The most common indication for intravitreal bevacizumab is exudative AMD. It is also used for the treatment of CNV due to other diseases (ocular histoplasmosis, myopia). Other indications are macular edema due to retinal vein occlusions, diabetes, post-cataract surgery, and proliferative diabetic retinopathy.

Exudative Age-related Macular Degeneration

Exudative AMD is the most common indication for intravitreal bevacizumab. Publications regarding intravitreal bevacizumab for the treatment of exudative AMD include six prospective studies,[45–50] one uncontrolled randomized trial,[51] nine retrospective studies,[52–60] and uncontrolled case series. The majority of the papers showed mean improvement in visual acuity and a reduction in macular thickness after intravitreal injection of bevacizumab. As yet there are no phase III clinical trials evaluating bevacizumab in AMD.

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In a retrospective study of 79 patients with a diagnosis of exudative AMD, affected eyes were injected monthly with 1.25mg of intravitreal bevacizumab until there were no signs of CNV. They were followed for eight weeks and showed an improvement in mean visual acuity from 20/200 to 20/80 and a mean reduction in central retinal thickness of 90µm.[37] It was found to be successful in eyes both with and without prior treatment. In 48 patients of whom 72% had received prior treatment with photodynamic therapy (PDT) and/or pegaptanib, there was significant improvement in visual acuity of 5.3 letters during a follow-up of 24 weeks; however, an average of 3.5 intravitreal injections of bevacizumab were required. In

patients without prior treatment, an improvement of 14.2 letters was seen.[61] Similar results have been observed in other studies.[62]

Studies using combination therapy are under way, with the goal of reducing the need for re-treatment and improving vision. A retrospective study of 24 eyes evaluated PDT combined with 1.25mg of intravitreal bevacizumab. The results showed two lines of visual acuity improvement at month seven, with 37% of patients requiring retreatment.[63]

Retinal Vein Occlusion

In central- and branch-vein occlusions, macular edema (perfused or non-perfused) is often treated with intravitreal bevacizumab. Grid-pattern laser photocoagulation was the first widely accepted treatment.[64–66] This has been the standard treatment and has shown benefit in selected cases of branch retinal venous occlusion (BRVO).[67] Intravitreal triamcinolone acetonide has also been used to treat BRVO,

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with several studies showing improvement in visual acuity and decreased macular thickness assessed by OCT.[68] However, the side effects of triamcinolone—including cataract formation and elevated intraocular pressure—call for alternative therapies such as anti-VEGF agents (in which these side effects are much less common), as VEGF levels are also elevated in patients with retinal vein occlusion.[69] In a study of 27 patients with BRVO who received intravitreal bevacizumab, visual acuity improved from 20/200 at baseline to 20/100 at three months. The mean central macular thickness improved from 478µm at baseline to 332µm.[70] Case reports of intravitreal bevacizumab for CRVO showed potential benefit of this treatment in short-term follow-up. In a study of 16 eyes with CRVO during a mean follow-up of three months, mean visual acuity improved from 20/600 to 20/200 at month one and to 20/138 at month three, associated with a reduction in central retinal thickness from 887 to 372µm in patients receiving at least one injection.[71] Additionally, bevacizumab has shown clinical efficacy in neovascular glaucoma, a common complication of ischemic CRVO. Multiple case reports demonstrate regression of neovascularization of the iris (NVI) and symptomatic improvement after injection of bevacizumab in the anterior chamber or vitreous cavity. Effects are seen within 48 hours and last at least four weeks.[72–74]

Proliferative Diabetic Retinopathy and Diabetic Macular Edema

Intravitreal bevacizumab in diabetic retinopathy was first used in patients with advanced proliferative diabetic retinopathy with vitreous hemorrhage that obscured the view for panretinal photocoagulation.[75–76] In these cases functional and anatomical recovery was seen one week after injection. In cases of extensive diabetic pre-retinal neovascular membranes, intravitreal bevacizumab has also been used as an adjunctive therapy before pars plana vitrectomy. Within one week the neovascular proliferations became inactive and contracted, and were easier to delaminate with less bleeding during vitrectomy.[77] Bevacizumab has been used for NVI in cases of proliferative diabetic retinopathy, similar to its use in neovascular glaucoma in CRVO. During follow-up all seven eyes showed regression of NVI within one week. Recurrence occurred in two eyes by the second month. Intraocular pressure was controlled in six out of seven eyes.[78]

In a study of 45 eyes with proliferative diabetic retinopathy, different doses of intravitreal bevacizumab were evaluated (from 6.2µg to 1.25mg per injection) and showed that all eyes with neovascularization on fluorescein angiography demonstrated a partial or complete regression of leakage within one week of injection. Interestingly, two contralateral eyes showed subtle regression of leakage, indicating a potential systemic effect of the treatment.[79] In a prospective study of patients with proliferative diabetic retinopathy treated with intravitreal injections of bevacizumab, a rapid regression of actively leaking neovascularization was observed, as well as significant improvement in mean visual acuity from 20/160 to 20/125+2 at three-month follow-up.[80] In a non-comparative case series, 51 patients with diffuse macular edema refractory to other treatments were studied. OCT measurements showed central retinal thickness decreased significantly from 501 to 416µm at six-weeks and 377µm at 12-week follow-up. Improvement in visual acuity of about one line was reported at six-week follow-up.[81]

Other Ocular Indications

Intravitreal bevacizumab has been used in cases of CNV secondary to high myopia. Initially, the intravitreal bevacizumab dose was 1–1.25mg, and it was reserved for cases of progression of CNV despite treatment with PDT, with or without intravitreal triamcinolone.[82,83] Initial results

> Patients with neovascularization secondary to sickle-cell retinopathy have responded positively to intravitreal bevacizumab.

were positive, showing CNV regression as well as visual acuity improvement. In cases of CNV secondary to angioid streaks and idiopathic juxtafoveal retinal telangiectasis, studies have shown a positive response with bevacizumab doses of 1.5 and 1.25mg, respectively.[84,85]

There are other potential indications for intravitreal bevacizumab besides the aforementioned examples, including other ocular diseases with retinal neovascularization. Patients with neovascularization secondary to sickle-cell retinopathy have responded positively to intravitreal bevacizumab.[86] The use of bevacizumab in retinopathy of prematurity is controversial. In cases of

refractory cystoid macular edema secondary to cataract surgery and posterior uveitis, observations suggest a positive response to intravitreal bevacizumab, indicating a potential anti-inflammatory effect of anti-VEGF therapy.[87,88]

Side Effects of Intravitreal Bevacizumab

A web survey was designed to investigate the side effects of intravitreal administration of bevacizumab from 70 centers in 12 countries. Of 7,113 injections given to 5,228 patients, there was one case of endophthalmitis (0.01%), one case of traumatic lens injury (0.01%), and three cases of retinal detachment (0.04%). Ocular adverse events that were reported included intraocular inflammation (0.14%), acute vision loss (0.07%), non-traumatic cataract progression (0.01%), and central retinal artery occlusion (0.01%). Potential drug-related systemic adverse events included an increase in blood pressure (0.21%), cerebrovascular accident (0.07%), deep venous thrombosis (0.01%), transient ischemic attack (0.01%), and death (0.03%).

> Since the discovery of vascular endothelial growth factor (VEGF) and its central role in ocular neovascular disease, the development of anti-VEGF therapies, including bevacizumab, will remain an important therapeutic tool for neovascular ocular diseases.

Large prospective clinical trials on pegaptanib and ranibizumab have reported that the risk of infectious endophthalmitis per injection is up to 0.16%, of traumatic cataract up to 0.07%, and of retinal detachment up to 0.17%.[89–91] There have been few reports on uveitis following intravitreal bevacizumab.[92,93] No published experimental study evaluating safety of intravitreal bevacizumab has yet shown evidence of toxicity with the doses used in clinical practice. Cases of retinal pigment epithelial (RPE) tears after intravitreal bevacizumab have been described.[94–96] This observation is most likely a side effect of CNV regression after treatment, as they have been reported after PDT, intravitreal pegaptanib, and ranibizumab.

Intravitreal bevacizumab doses are 200- to 400-fold lower than systemic doses and, thus far, the systemic adverse events reported in oncological trials have not been reported with intravitreal use.

Conclusion

Since the discovery of VEGF and its central role in ocular neovascular disease, the development of anti-VEGF therapies, including bevacizumab, will remain an important therapeutic tool for neovascular ocular diseases. The National Institutes of Health (NIH) are currently conducting the Comparative AMD Treatment Trial (CATT), which will compare intravitreal bevacizumab and ranibizumab in patients with AMD. Research into other drugs—including tyrosine kinase receptor inhibitors, which inhibit downstream effects of VEGF—have been effective in the treatment of CNV in early studies. In addition, there are other growth factors, including pigment epithelium-derived factor, that are being investigated. Combination therapies are also gaining importance in trying to achieve less frequent treatments. Future studies will be crucial for optimization in the treatment of each ocular condition. ■

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