

Bevacizumab in the Treatment of Ocular Disease

A reduced cost and increased half-life may find bevacizumab as an attractive worldwide treatment choice.

BY DANTE J. PIERAMICI, MD; AND ROBERT L. AVERY, MD

In the 1960s, Bob Dylan said, “The times they are a-changin’.” This statement is certainly appropriate today when considering the treatment of retinal and choroidal neovascularization (CNV). From the 1980s to the late 1990s, the only effective weapon in the treatment of such neovascularization was laser photocoagulation. This destructive therapy was rarely appropriate for subfoveal CNV lesions. Photodynamic therapy (PDT) attempted to use the laser in a less destructive form and salvage the overlying neurosensory retina. Despite the efficacy of this treatment, the average patient lost vision — although less than without treatment. The shortcomings of these and other attempts to treat retinal neovascularization have fostered a continued drive for better management. In 2006, we resolutely enter the era of antiangiogenic therapy in the treatment of retinal diseases.

Michaelson et al¹ first proposed that growth factors play a role in the pathophysiology of retinal vascular disease in 1948. He suggested that factor “X” was responsible for initiating and maintaining angiogenesis. Today, we know that Michaelson’s factor X is, in part, vascular endothelial growth factor (VEGF). The identification and cloning of VEGF in the 1980s and the subsequent development of anti-VEGF antibodies prompted the study of VEGF and its role in ocular disease.² Various studies have

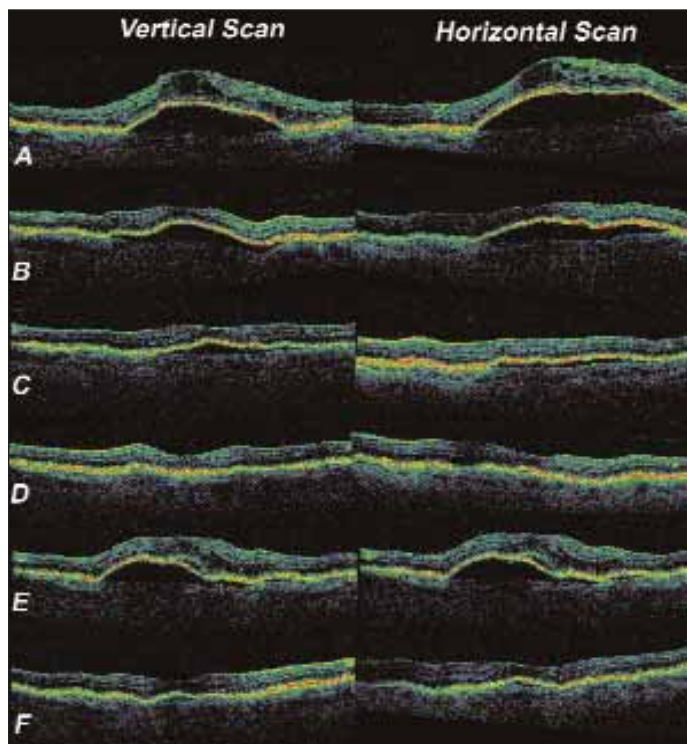


Figure 1. OCT images of patient also featured in Figure 3: A) prior to bevacizumab; B) 1 week following 1.25 mg intravitreal bevacizumab; C) 1 month following first injection; D) 1 month following second injection; E) after holding injection for 6 weeks, patient develops recurrent leakage and decreased vision; F) following reinjection. Vision improved from 20/100 to 20/50.

demonstrated not only a correlation between VEGF levels and proliferative diabetic retinopathy (PDR) severity, but also a reduction in levels after successful laser treatment of this disease. VEGF is also implicated in the neovascular stages of age-related macular degeneration (AMD). VEGF inhibition in animal models and humans has proven to reduce CNV and its associated vascular leakage, strengthening the role of this agent in the pathogenesis of CNV.

Bevacizumab (Avastin; Genentech, San Francisco) is a humanized monoclonal antibody to VEGF; it is designed for intravenous administration and approved for the treatment of colorectal cancer. Ranibizumab (Lucentis; Genentech) is a related molecule consisting only of the fragment antigen binding (Fab) that binds the VEGF receptor. Two large phase 3 clinical trials have demonstrated the safety and efficacy of ranibizumab in treatment for neovascular AMD. Ranibizumab is the first treatment for subfoveal CNV that affects a mean increase in visual acuity in treated patients.

Rosenfeld first reported the use of bevacizumab systemically and intravitreally in the treatment of macular degeneration.^{3,4} This work revealed a marked biologic effect following intravitreal injection and potentially circumvented the possible toxicity of systemic administration.

BEVACIZUMAB: STRUCTURE, BINDING AND OCULAR PENETRATION

Ranibizumab and bevacizumab are derived from the same murine antibody as VEGF. Ranibizumab was developed specifically for the eye after preclinical primate studies⁵ showed full penetration of all retinal layers by Fab fragments the size of ranibizumab after intravitreal injection. Lack of retinal penetration of a full length antibody, however, occurred due to blockage at the internal limiting membrane (ILM).

We have recently studied the penetration of intravitreal bevacizumab in rabbits; full-thickness neurosensory retinal penetration was seen within 24 hours, challenging the results of Mordenti et al.⁶ Our contradictory results may be explained by the use of different species or different epitopes, as the immunoglobulin G (IgG) used in the Mordenti study was developed against human epidermal growth factor 2 instead of VEGF. Another reason may relate to dosage. In the Mordenti study, an intravitreal dose of 25 μ g was administered (fiftyfold less than is clinically used in humans), while we tested doses ranging from 250 μ g to 2.5 mg and found full-thickness retinal penetration. The clinically observed biologic effect of intravitreal bevacizumab may relate to the anatomy of the human foveola where the ILM is greatly attenuated or absent.

A clinically important difference between bevacizumab

and ranibizumab may be the half-life in the vitreous and bloodstream. Ranibizumab has been well studied, and the intravitreal half-life in primates is approximately 3.2 days.⁵ Although at this time there are no published reports on pharmacokinetics of intravitreal bevacizumab, there are studies of similar molecules such as trastuzumab (Herceptin; Genentech) — a humanized monoclonal IgG with the same molecular weight as bevacizumab — that demonstrated an intravitreal half-life of 5.6 days.⁵ It is likely that the vitreous and serum half-life of bevacizumab will be longer than that of ranibizumab. This may be advantageous because of less frequent dosing versus ranibizumab, however, the longer systemic half-life may contribute to a higher risk of systemic side effects.

CLINICAL APPLICATIONS OF BEVACIZUMAB

AMD

Our group began using intravitreal bevacizumab in the treatment of subfoveal AMD in the summer of 2005, shortly after learning of Rosenfeld's initial intravitreal injections.^{4,7} We reported our first consecutive series of patients treated for this indication in March.⁸ The preliminary indication for treatment in our series was active subfoveal CNV in patients who failed previous treatment with either pegaptanib (Macugen; OSI Eyetech, Melville, NY/Pfizer, New York, NY), PDT or a combination of triamcinolone and PDT. Failure was defined as progressive loss of vision without obvious reduction in CNV leakage. These patients were offered intravitreal bevacizumab after extensive discussion about off-label triamcinolone use and potential ocular and systemic risk factors.

Like ranibizumab, bevacizumab (intravitreal dose 1.25 mg) had a rapid, unequivocal but variable biologic effect in our patients. In some cases, a single intravitreal injection resolved retinal edema, subretinal fluid and subretinal pigment epithelium (RPE) fluid within 1 week. In other cases, primarily when large pigment epithelial detachments were present, resolution would occur weeks to months after initial injection. This showed that many patients may require more than one injection to maximize the effect.

In our initial retrospective, uncontrolled, consecutive series of 79 patients (81 eyes) treated with intravitreal bevacizumab, 30 of 81 eyes demonstrated complete resolution of retinal edema, subretinal fluid and pigment epithelial detachments at 4 weeks postinjection. Of 51 eyes, 25 eyes had complete resolution of retinal thickening, subretinal fluid, and pigment epithelial detachments at 8-week follow-up. The central 1 mm of retinal thickness — as measured by optical coherence tomography (OCT) — was found to decrease from baseline by a mean of 61 μ m at 1 week; 92 μ m at 4 weeks; 89 μ m at 8 weeks; and 67 μ m at 12 weeks ($P < .0001$ at each time point except 12 weeks,

$P < .01$). A biologic effect was seen in all subtypes of CNV treated (predominantly classic, minimally classic and occult). In an attempt to reduce the risk of systemic side effects, a lower 125- μ g dose has been administered with effective reduction in the CNV leakage. Concerns over reduced durability persist, however.

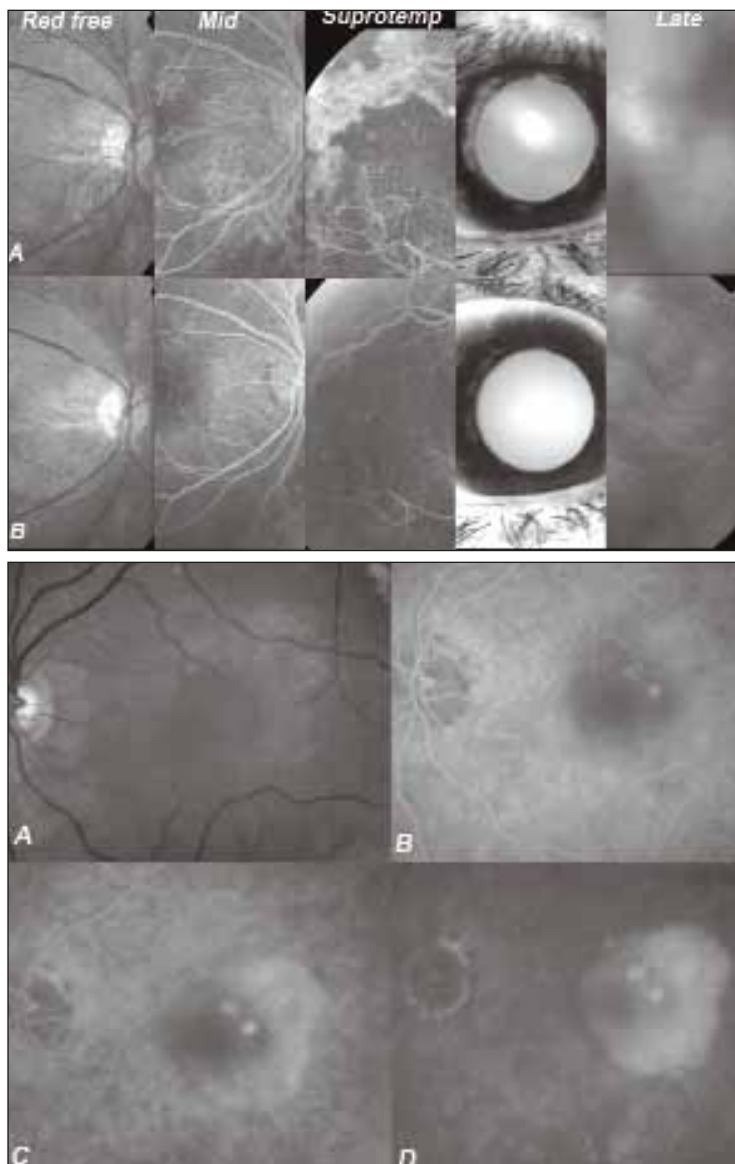
The optimum dosing schedule has yet to be determined and appears to case-dependent. We have favored treatment on as needed protocol, using the OCT, visual acuity and fluorescein angiographic findings to guide retreatment. Following initial injection, if obvious retinal, subretinal, or sub-RPE fluid persists, additional treatment was recommended. If the fluid resolved completely, however, treatment was withheld. In our experience, recurrences tended to happen 6 weeks to 8 weeks following initial injection, although several patients have not experienced recurrence 6 months after their only injection. It is reassuring that, at least in this small series with limited follow-up, recurrence could be effectively retreated without obvious sequelae.

In our original series at 4 weeks and 8 weeks, mean visual acuity improved from 20/200 to 20/125 ($P < .0001$). The median vision improved from 20/200 to 20/80- at 4 weeks and from 20/200 to 20/80 at 8 weeks. These vision measurements were not standardized or refracted, and bias may have existed. Because most cases received previous treatments for subfoveal CNV, few were recent-onset lesions. Better visual results might be possible with newer lesions prior to the onset of irreversible neurosensory destruction.

Bevacizumab appears to be safe and well tolerated. In our series, there were no adverse ocular or systemic side effects detected. All patients were monitored at baseline, 1 week and monthly following injection. Patients underwent ocular examination, review of ocular and systemic symptoms and measurement of blood pressure. Unlike systemic bevacizumab in which hypertension is a common side effect, no case of remarkable elevation of blood pressure was detected in our series. Single and multiple intravitreal injections were well tolerated in all patients.

No patient developed uveitis, endophthalmitis, ocular toxicity, thromboembolic

events and no patients died. We have treated more than 350 patients with intravitreal bevacizumab and the only obvious side effect, systemic or ocular, was one case of mild uveitis that followed the fourth intravitreal injection.



Figures 2,3. (Figure 2) Patient with bilateral severe high risk profile diabetic retinopathy and neovascularization of the iris. Patient has already received extensive PRP. Row A is prior to bevacizumab. Patient has widespread neovascularization of the disc, neovascularization elsewhere, macular edema and neovascularization of the iris without glaucoma. Row B shows 1 week following 1.25 mg intravitreal bevacizumab. There is marked regression of all neovascularization (NVD, NVE and NVI), improved vision and reduction in macular edema. (Figure 3) The patient presents with reduced vision in the left eye and disciform scar in the fellow eye. Angiography reveals a retinal angiomatous proliferative lesion.

CLINICAL APPLICATIONS OF BEVACIZUMAB, CONTINUED

Diabetic Retinopathy and Other Retinovascular Diseases

The role of VEGF has been firmly established in the pathophysiology of diabetic retinopathy.² Elevated VEGF has been associated with all stages of retinopathy, and the highest levels are seen in PDR.⁹ In addition to proliferative retinopathy, VEGF likely plays a role in the development of diabetic macular edema (DME), as VEGF is a potent vascular permeability factor. Prior to the advent of laser photocoagulation, a majority of patients who developed PDR and macular edema would go on to experience moderate-to-severe vision loss. Unlike laser treatment for AMD, pan-retinal photocoagulation (PRP) for the treatment of neovascularization has been extremely effective. Prior to PRP, blindness would occur in most patients who developed high-risk proliferative disease. With timely treatment, this is a minimal risk.

There are drawbacks to PRP, and patients may experience a decrease in central, peripheral and/or night vision. In addition, response to treatment may not be ideal. Patients with advanced stages of DME or PDR may be resistant to the most extensive of PRP treatments. When anterior segment or vitreous opacity (eg, vitreous hemorrhage) is present, one must await clearing of the opacity. This delay will likely allow for disease progression and recurrent hemorrhage.

MARKED REGRESSION

For the last 8 months, we have offered intravitreal bevacizumab to patients with advanced proliferative disease. Following a single 1.25-mg injection, we have witnessed marked regression of retinal and iris neovascularization, sometimes within days.¹⁰ In these cases, it appears that there is not only a reduction of leakage from the neovascularization, but variable fibrous regression of vessels as well; however, with time, many of these regressed vessels will recur unless retreated. Following a single intravitreal injection of 1.25 mg, we witnessed a possible response in the fellow eye (noninjected eye), underscoring the possibility of systemic absorption of the medication. Concerns over potential systemic complications compelled us to attempt lower doses, and again, we have witnessed significant reduction in retinal and iris neovascularization following doses as low as 6.25 ug/mL, however, the durability of response is likely reduced.

The Early Treatment of Diabetic Retinopathy Study (ETDRS) showed that laser photocoagulation, although effective in reducing the chance of moderate visual loss, rarely led to vision improvement in patients with DME, when the center of the macula is involved. The antiperme-

ability effects of an anti-VEGF agent provide an intriguing strategy for the management of DME. In some cases, 1.25 mg of intravitreal bevacizumab results in rapidly reduced DME and concomitantly increased vision, and in other cases the response was less obvious. The reason for this variability will require further study, but it may reflect differences in the pathophysiology of DME in various patients.

We have found short-term use of bevacizumab to be particularly helpful as a surgical adjunct. In cases requiring vitrectomy for complications of PDR, intravitreal injection of bevacizumab 1 or 2 weeks presurgery appears to reduce intraoperative bleeding, facilitating membrane removal.

CONCLUSIONS

Pegaptanib was the first anti-VEGF agent to receive FDA approval for intraocular use, but, its efficacy in the treatment of neovascular AMD does not match that of ranibizumab, and it is likely to be used sparingly once ranibizumab is available. Initial experience with bevacizumab — in our practice — has been encouraging and suggests a biologic response similar to what is reported for ranibizumab.

If bevacizumab proves to have similar safety and efficacy to ranibizumab, the appreciably reduced cost and increased half-life could make bevacizumab an attractive choice worldwide. ■

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1. Michaelson IC. The mode of development of the vascular system of the retina, with some observations on its significance for certain retinal diseases. *Trans Ophthalmol Soc UK*. 1948;68:137-180.
2. Ferrara N. Vascular endothelium growth factor: Basic science in clinical progress. *Endocr Rev*. 2004; 25:581-611.
3. Michels S, Rosenfeld PJ, Puliafito CA, Marcus EN, Denkatraman AS. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: Twelve week results of uncontrolled open label clinical study. *Ophthalmology*. 2005;112:1035-1047.
4. Rosenfeld PJ, Moshfeghi AA, Puliafito CA. Optical coherence tomography findings after intravitreal injection of bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmic Surg Lasers Imaging*. 2005;36:331-335.
5. Mordenti J, Cuthbertson RA, Ferrara N, et al. Comparisons of the intraocular tissue distribution pharmacokinetics and safety of 125 I-labeled Fab antibodies in rhesus monkeys following intravitreal administration. *Toxicol Pathol*. 1999;27:536-544.
6. Shahar J, Avery RL, Heilweil G, et al. Electrophysiologic and retinal penetration in studies following intravitreal injection of bevacizumab (Avastin). *Retina*. 2006;26:262-269.
7. Rosenfeld PJ, Fung AE, Puliafito CA. Optical coherence tomography findings after intravitreal injection of bevacizumab (Avastin) for macular edema from central retinal vein occlusion. *Ophthalmic Surg Lasers Imaging*. 2005;36:336-339.
8. Avery RL, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology*. 2006;113:363-372.
9. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluids of patients with diabetic retinopathy and other retinal disorders. *New Engl J Med*. 1994;331:1480-1487.
10. Avery RL. Regression of retinal and iris neovascularization following intravitreal bevacizumab (Avastin). *Retina*. 2006;26:352-354.