

Optical Coherence Tomography Findings After an Intravitreal Injection of Bevacizumab (Avastin®) for Neovascular Age-Related Macular Degeneration

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Abstract. To determine whether intravitreal bevacizumab could improve optical coherence tomography and visual acuity outcomes in a patient with neovascular age-related macular degeneration who was responding poorly to pegaptanib therapy, an intravitreal injection of bevacizumab (1.0 mg) was given. Within 1 week, optical coherence tomography revealed resolution of the subretinal fluid, resulting in a normal-appearing macular contour. The improved macular appearance was maintained for at least 4 weeks, and visual acuity remained stable. No inflammation was observed. An intravitreal injection of bevacizumab may provide an effective, safe, and inexpensive option for patients with

age-related macular degeneration who are losing vision secondary to macular neovascularization. [*Ophthalmic Surg Lasers Imaging* 2005;36:331-335.]

INTRODUCTION

Vascular endothelial growth factor (VEGF) has been implicated as the major angiogenic stimulus responsible for neovascularization in age-related macular degeneration (AMD).^{1,2} Inhibition of VEGF using intravitreal injections of pegaptanib sodium (Macugen; Eyetech Pharmaceuticals, Inc., New York, NY) was superior to sham-treated controls in a Phase II/III trial, but the average patient treated with pegaptanib still lost vision.³ Ranibizumab (Lucentis; Genentech Inc., San Francisco, CA) is another inhibitor of VEGF designed specifically for ophthalmology and is currently in Phase III clinical trials for neovascular AMD.⁴ Ranibizumab is derived from a larger molecule known as bevacizumab (Avastin; Genentech Inc.), which was designed as an intravenous anti-angiogenic drug for oncology.⁵

Bevacizumab is approved for the treatment of metastatic colorectal cancer, and a study using off-label intravenous bevacizumab for neovascular AMD showed promising results.⁶ However, the use of intravitreal bevacizumab in humans has never been reported. This article describes a patient who received a single intravitreal injection of bevacizumab as a salvage treatment after having experienced disease progression following photodynamic therapy with intravitreal triamcinolone acetonide and pegaptanib therapies.

CASE REPORT

A 63-year-old woman developed subfoveal, predominantly classic choroidal neovascularization (CNV) in her left eye and was treated with photodynamic therapy in combination with an intravitreal injection of triamcinolone acetonide in August 2004. In February 2005, she developed recurrent CNV in her left eye. The patient refused additional photodynamic therapy because of the poor visual acuity that resulted in her right eye after retreatment with photodynamic therapy, and she elected to receive an intravitreal injection of

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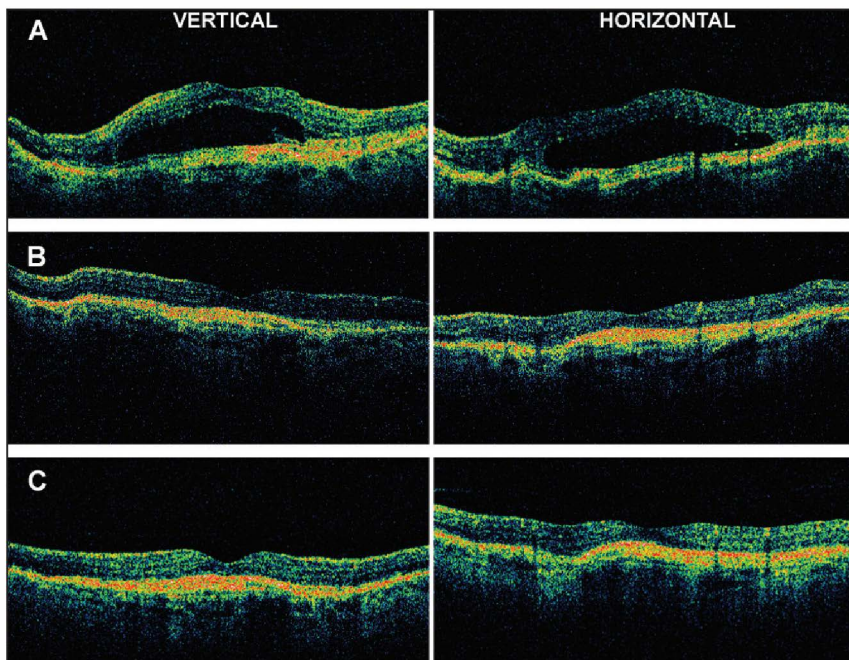


Figure 1. Vertical (left side) and horizontal (right side) 6 mm optical coherence tomography scans and 1 mm central retinal thickness measurements at (A) baseline (582 μm), (B) week 1 post-injection (180 μm), and (C) week 4 post-injection (193 μm).

pegaptanib to her left eye instead. She was observed by one of the authors (PJR) during the next 12 weeks, and after two injections of pegaptanib, her visual acuity decreased from 20/200 to 20/400, optical coherence tomography (OCT) revealed increasing fluid under the retina (Fig. 1A), and fluorescein angiography showed an enlarging predominantly classic neovascular lesion associated with leakage (Fig. 2A).

The patient was offered additional pegaptanib therapy, PDT, or the possibility of participating in the Systemic Avastin for Neovascular AMD (SANA) Study at the Bascom Palmer Eye Institute. She elected to be screened for the SANA Study, but decided not to participate on the day of screening because of the need for frequent follow-up visits to Miami to monitor for adverse events. She was then offered an off-label intravitreal injection of bevacizumab into her left eye with

follow-up at one of our satellite offices. After extensive discussions, she signed a non-study consent for the off-label intravitreal injection of bevacizumab.

The eye was prepared using a standard protocol that employed a sterile lid speculum and topical 5% povidone-iodine. Approximately 1.0 mg of bevacizumab was injected into her left eye (0.04 mL of commercially available bevacizumab at a concentration of 25 mg/mL). Her visual acuity, as determined at this screening visit using an ETDRS (Early Treatment Diabetic Retinopathy Study) chart at 2 meters, was equivalent to a Snellen acuity of 20/125.

She returned 1 week post-injection, reporting that the visual distortion in her left eye had resolved. Examination revealed no evidence of ocular inflammation, and OCT revealed complete resolution of the subretinal fluid (Fig. 1B). Four weeks post-injec-

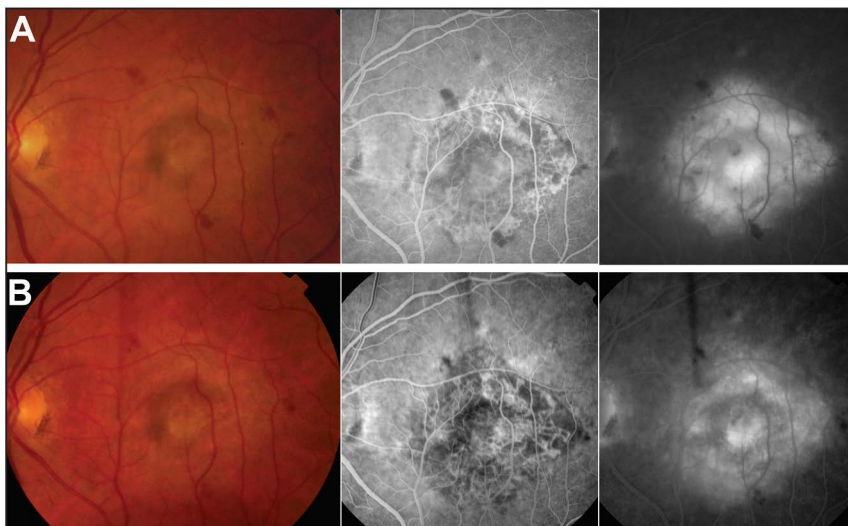


Figure 2. Color fundus photographs with early and late-phase fluorescein angiographic images at (A) baseline and (B) week 4 post-injection.

tion, the ETDRS visual acuity was stable at 20/125. OCT revealed resolution of the subretinal fluid and a near-normal macular contour (Fig. 1C). There was no evidence of angiographic leakage (Fig. 2B). Her blood pressure remained unchanged during the 4 weeks at 120/70. No additional treatment was given at this visit. Although the patient was observed for only 4 weeks after the injection of bevacizumab, there was no evidence of cataract progression. This was the first patient with neovascular AMD who received an injection with bevacizumab by one of the authors (PJR).

DISCUSSION

This is the first report of an injection of bevacizumab into a human eye. One week after the injection, there was no evidence of inflammation and a dramatic improvement in the cross-sectional anatomy of the macula was observed using OCT. At 4 weeks, this improvement on OCT was maintained and fluorescein angiography demonstrated an absence of leakage from the macular neovascularization. We do not know yet whether this type of response is generally applicable to other patients with neovascular AMD or whether

this treatment is safe, but for those patients with AMD who are losing vision due to leakage from neovascularization despite treatment with approved therapies, an intravitreal injection of bevacizumab may provide another potential treatment option.

Patients must be made aware of all of the potential risks of bevacizumab therapy, particularly the risks of hypertension and thromboembolic events.⁶ Compared with intravenous bevacizumab, intravitreal bevacizumab has certain advantages. The most obvious advantage is that approximately 400-fold less drug is used for an intravitreal dose compared with an intravenous dose. This provides both a safety and cost advantage over intravenous bevacizumab therapy. Although the cost for an intravenous bevacizumab dose at 5 mg/kg is approximately \$2,200 for a 70- to 80-kg patient using 100-mg vials at a cost of \$550 per vial, the cost of a 1-mg intravitreal dose is only \$5.50. Therefore, the intravitreal injection of bevacizumab has a significant cost advantage over other pharmaceutical treatments such as verteporfin and pegaptanib when comparing unit dosing.

Why wasn't bevacizumab used for the treatment of

neovascular AMD prior to this report? The most likely explanation is that the pre-clinical data obtained with bevacizumab suggested that the full-length antibody would not penetrate the retina adequately and, as a result, insufficient VEGF would be inhibited to have a therapeutic effect.⁷ This was a reasonable conclusion based on the published observations that when ranibizumab, the antibody fragment derived from bevacizumab, was injected into the vitreous of normal rhesus monkeys, it was able to penetrate the full thickness of the retina, whereas a full-length antibody showed only limited penetration through the inner retina. This observation was consistent with the belief that a protein with a molecular weight of 150 kD would be too large to penetrate the inner limiting membrane of the retina.

We have described a case of neovascular AMD with a positive therapeutic response following an intravitreal injection of the full-length antibody known as bevacizumab. One possible explanation for why we observed a response is that larger molecules might penetrate the aged human retina better than the non-human primate retina. Alternatively, limited penetration by a full-length antibody through the inner retina may be sufficient to bind a limited amount of VEGF and result in a therapeutic effect. One other possibility is that there may be VEGF in the vitreous cavity that contributes to the growth and leakage of the neovascularization, and inhibition of that VEGF is sufficient to achieve a therapeutic effect.

Finally, it is possible that the monkey study was flawed because the investigators never studied the retinal distribution of a full-length anti-VEGF antibody. Instead of using bevacizumab, they used an antibody against the human epidermal growth factor receptor 2 (HER2) known commercially as Herceptin (Genentech Inc.). In their experiments, they compared the retinal penetration of an anti-VEGF antibody fragment (48 kD) with the penetration of the full-length antibody against HER2 (148 kD). Both proteins were radiolabeled and injected into the vitreous of the rhesus monkeys, and the retinal penetration of these proteins was monitored after enucleation using autoradiography. The anti-VEGF antibody fragment penetrated the full thickness of the retina, whereas the full-length anti-HER2 antibody penetrated only into the inner retina. It is possible that the anti-HER2 antibody became bound to the cell surface HER2 antigen present within the

inner retina,⁸ thereby preventing deeper penetration of the antibody even though excess unlabelled anti-HER2 antibody was added to supposedly saturate these binding sites within the inner retina.

Whatever the explanation, the results we have observed following the intravitreal injection of bevacizumab are provocative and require additional investigation. Further studies should include a dose-escalation strategy so that a dose-response curve can be established, but an intravitreal bevacizumab dose of 1.0 mg is a good first approximation for the appropriate dose. The current Phase III trials with ranibizumab use monthly injections of 0.3 or 0.5 mg. Because ranibizumab has a molecular weight approximately one-third that of bevacizumab, the equivalent number of bevacizumab molecules would require a dose of 0.9 to 1.5 mg. However, because each molecule of bevacizumab has two antigen-binding arms compared with a single site in ranibizumab, which is an antibody fragment, a lower dose might suffice. But, ranibizumab has been genetically engineered and affinity matured, resulting in a 140-fold higher binding affinity at its single site compared with a single bevacizumab site⁹; therefore, more bevacizumab might be needed. If bevacizumab does not penetrate the retina as well as ranibizumab, then more might be needed, but because the half-life of bevacizumab in the vitreous cavity is probably twice as long as ranibizumab, less might be needed.¹⁰

In consideration of all known properties of bevacizumab, a dose of 1 to 1.25 mg seems to be a dose around which a dose-response study can be designed. This dose can be conveniently injected using 0.04 to 0.05 mL of the commercially supplied bevacizumab, which is not known to contain preservatives or additives that may be toxic to the retina.

A formal prospective study is necessary to determine the safety and efficacy of intravitreal bevacizumab for the treatment of neovascular AMD. In the future, from a cost-benefit perspective, it is entirely possible that intravitreal injections of bevacizumab may become the preferred first-line therapy for the treatment of neovascular AMD.

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