

Intravitreal Bevacizumab for the Management of Choroidal Neovascularization in Age-related Macular Degeneration

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• **PURPOSE:** To investigate the efficacy and safety of intravitreal bevacizumab for managing choroidal neovascularization (CNV) due to age-related macular degeneration (AMD).

• **DESIGN:** Prospective interventional case series.

• **METHODS:** Seventeen eyes of 17 patients with subfoveal CNV due to AMD participated in this study at the American University of Beirut Ophthalmology Clinics. All patients had failed, refused, or were not eligible for photodynamic therapy. All eyes received a baseline eye examination, which included best-corrected visual acuity (BCVA), dilated fundus examination, ocular coherence tomography (OCT) imaging, and fluorescein angiography. An intravitreal injection of bevacizumab (2.5 mg/0.1 ml) was given at baseline and followed by two additional injections at four-week intervals. BCVA, OCT, and fluorescein angiography were repeated four weeks after each injection. Main outcome measures were improvement in BCVA and central retinal thickness (CRT).

• **RESULTS:** Mean baseline BCVA was 20/252 (median 20/200), and baseline CRT was 362 μ m (median 350 μ m). Improvement in VA and CRT occurred by the fourth week. At 12 weeks, mean BCVA was 20/76 ($P < .001$) and median BCVA was 20/50 ($P < .001$). Both mean and median CRT decreased to 211 μ m ($P < .001$). Thirteen (76%) of 17 eyes had total resolution of subretinal fluid, and four eyes (24%) had BCVA better than 20/50. No systemic or ocular side effects were noted at any time.

• **CONCLUSION:** Eyes with CNV due to AMD treated with intravitreal bevacizumab had marked anatomic and

visual improvement. Further studies are necessary to confirm the long-term efficacy and safety of this treatment. (Am J Ophthalmol 2006;142:1–9. © 2006 by Elsevier Inc. All rights reserved.)

AGE-RELATED MACULAR DEGENERATION (AMD) IS A leading cause of legal blindness in the industrialized world.¹ Although neovascular AMD is less prevalent than atrophic AMD, it accounts for most cases with severe visual loss from AMD.^{1–3} Vascular endothelial growth factor (VEGF) has been implicated in the choroidal neovascularization (CNV) of AMD.⁴ VEGF helps promote endothelial cell growth and increases vascular permeability.^{4,5}

Standard treatment options for CNV include argon laser photocoagulation and photodynamic therapy (PDT) using verteporfin. The Macular Photocoagulation Study showed that well-defined or “classic” subfoveal CNV was amenable to argon laser photocoagulation.^{6–9} However, this procedure results in irreversible photoreceptor injury that usually causes a central scotoma.⁹ Later, large multicenter studies showed that PDT was effective in decreasing the probability of moderate and severe visual loss from predominantly classic subfoveal CNV.^{10–12} Although PDT was designed to minimize damage to the retina and retinal vessels, a patient may continue to lose vision before stabilizing.^{11,12}

In December 2004, the US Food and Drug Administration approved intravitreal injection of pegaptanib, a 28-base anti-VEGF aptamer, for the management of CNV. Although pegaptanib-treated eyes continued to lose vision during the first year of the trial, they fared better than controls.^{13,14} Another anti-VEGF agent currently in phase III clinical trials for neovascular AMD is ranibizumab, a chemically modified product of bevacizumab that is affinity-matured to have higher affinity for VEGF (Miller J, unpublished data, presented at American Society of Retina Specialists Annual Meeting, July 2005). Bevacizumab is a humanized monoclonal antibody that inhibits all isoforms

See accompanying Editorial on page 141.

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of VEGF and is approved for treatment of colorectal cancer.¹⁵ Recently, bevacizumab was used to treat CNV due to AMD. Michels and associates¹⁶ showed that intravenous bevacizumab administered in two or three infusions at a dose of 5 mg/kg every two weeks decreased central retinal thickness (CRT) and improved vision. Later, Rosenfeld and associates¹⁷ presented a case report of a single eye that had improved CRT and visual acuity four weeks after an intravitreal injection of 1.25 mg of bevacizumab.

We treated 17 eyes with CNV due to AMD with intravitreal bevacizumab. We report on the anatomic and visual acuity results after 12 weeks of follow-up.

METHODS

STARTING AUGUST 2005, EYES WITH SUBFOVEAL CNV DUE to AMD were considered for intravitreal bevacizumab. Patients were offered this treatment if they were not eligible for PDT, refused PDT, or had not responded to PDT. Eyes not eligible for PDT were those with minimally classic CNV greater than four disk areas or those with CNV that is more than 50% obscured by blood. Nonresponse to PDT was considered if the subfoveal CNV continued to grow with loss of visual acuity after three sessions. Eyes with occult CNV were also considered for treatment if there was evidence of subretinal hemorrhages on fundus examination or the patient noted recent decrease in visual acuity over the past 12 weeks. The hospital administration at the American University of Beirut Medical Center gave permission for the use of intravitreal bevacizumab as a compassionate treatment in a situation that would otherwise result in severe visual loss. All patients who were considered for intravitreal bevacizumab treatment had a thorough discussion about the possible benefits and complications. All patients signed a consent form for the off-label intravitreal injection of bevacizumab. The study was in adherence to the tenets of the Declaration of Helsinki.

Initial examination included best-corrected visual acuity (BCVA) using Snellen acuity charts, slit-lamp examination of the anterior segment, dilated fundus examination, and fluorescein angiography. Eyes with better than 20/50 visual acuity were not considered for treatment. Baseline 1-mm CRT was measured for all eyes using ocular coherence tomography (OCT) macular retinal mapping (Stratus OCT, Carl Zeiss Meditec, Dublin, California, USA). This map was created from six consecutive slow diagonal 6-mm scans that intersected at the fovea. Retinal thickness was measured automatically by the OCT software, and this was the distance between the vitreoretinal interface and the anterior surface of the retinal pigment epithelium. Because AMD patients may have difficulty fixating, the fundus image generated by the OCT machine during the procedure was used to center the scan at the fovea for each

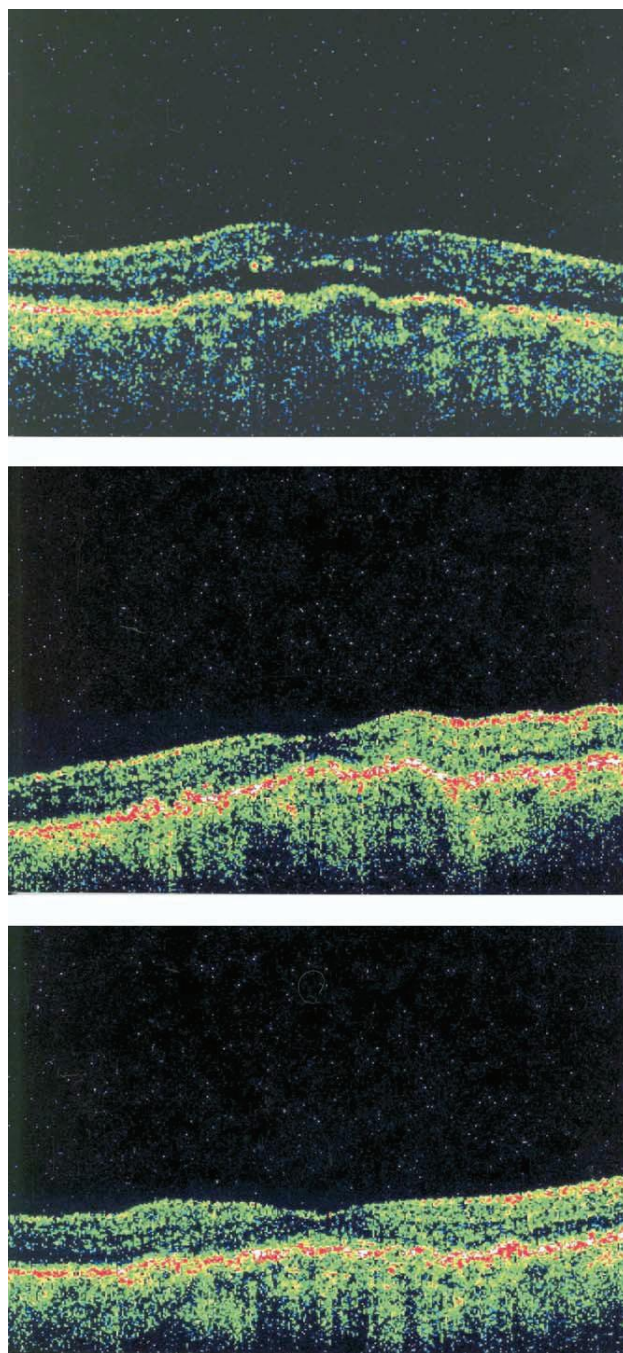


FIGURE 1. Ocular coherence tomography (OCT) scans and central retinal thickness (CRT) measurements for an eye with subfoveal choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) that had complete resolution of subretinal fluid after the first intravitreal injection of bevacizumab. (Top) Baseline CRT is 236 μm with a visual acuity of 20/50. (Middle) One week after injection, CRT is 184 μm . (Bottom) Four weeks after injection, CRT is 187 μm with visual acuity of 20/50. OCT at eight and 12 weeks remained unchanged, but visual acuity was 20/40.

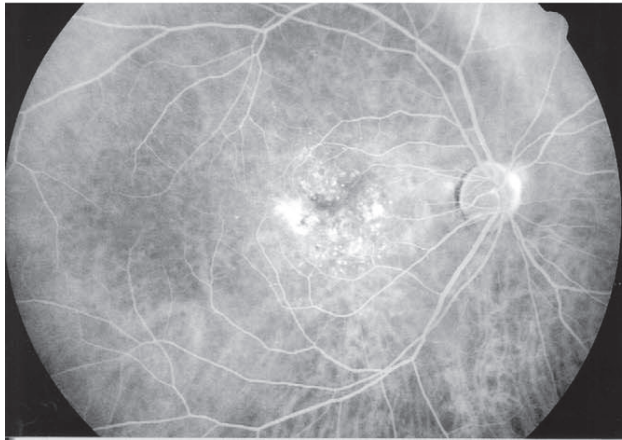
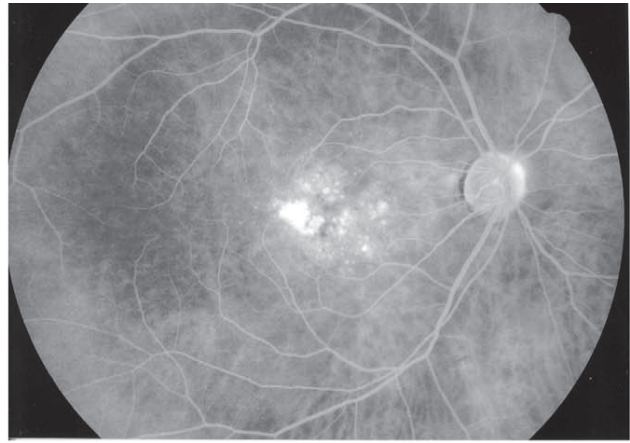
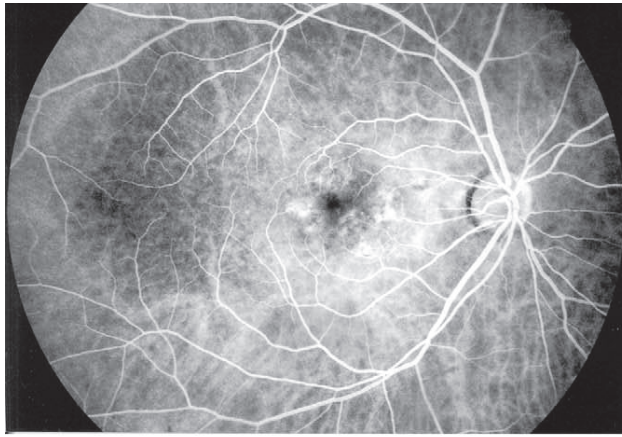


FIGURE 2. Fluorescein angiographic changes in choroidal neovascularization (CNV) for the eye in Figure 1 after the first intravitreal injection of bevacizumab. Early-phase (Top left) and late-phase (Top right) angiograms before treatment show occult CNV. (Bottom) Late-phase angiogram four weeks after treatment with resolution of late leakage. Follow-up angiography at eight and 12 weeks continued to show no leakage.

examination. All OCT examinations at baseline and at follow-up were done by the same person (A.S.).

All patients had blood pressure measurements at every visit. They were also monitored for symptoms of possible thromboembolic events.

The hospital pharmacy divided a 100-mg (4-ml) vial of bevacizumab (Genentech Inc, San Francisco, California, USA) into 20 1-ml syringes using aseptic techniques and under a laminar flow hood. Therefore, each syringe contained 5 mg, or 0.2 ml, of bevacizumab. The syringes were stored at 4°C for no longer than 14 days. After that time, remaining syringes were discarded because sterility could not be considered without further sterility testing.¹⁸ No stability testing was done to determine if bevacizumab remained stable in polypropylene syringes during the 14-day period.

The eye to be treated was prepared with 5% povidone-iodine solution. Anesthesia was administered as a subconjunctival injection of lidocaine 2% in the inferotemporal quadrant approximately 3 to 4 mm from the limbus. Enough anesthetic was injected to form a small bleb in the area where the intravitreal injection was to be given. Using a 30-gauge needle, 0.1 ml (2.5 mg) bevacizumab was injected intravitreally through the pars plana 3.5 mm from the limbus. If the intraocular pressure was greater than 25 mm Hg or the optic nerve head was not adequately perfused 20 minutes after the injection, a paracentesis was performed. Tobra-

mycin eye ointment (Alcon, Puurs, Belgium) was instilled in the treated eye, and a light patch was applied. Patients were instructed to unpatch the eye the next day and use topical ciprofloxacin (Alcon, Puurs, Belgium) three times a day for three days.

A similar intravitreal injection of bevacizumab was administered to all eyes at four and eight weeks of follow-up even if there was total resolution of subretinal fluid and retinal pigment epithelial detachment.

Patients were examined at one week and four weeks after each injection. BCVA was measured at each visit along with slit-lamp examination of the anterior segment and dilated fundus examination. OCT and fluorescein angiography were repeated at least at the four-week follow-up. Ocular side effects that were monitored were decrease in vision, rise in intraocular pressure, cataract formation, inflammation, bacterial endophthalmitis, retinal detachment, vitreous hemorrhage, and changes on fundus examination or fluorescein angiography.

The main outcome measures were improvement in visual acuity and decrease in CRT. Snellen acuities were converted to the logarithm of the minimum angle of resolution (logMAR) to facilitate statistical analysis. The paired Student *t*-test was used to compare the mean visual acuity and CRT at weeks four to 12 after treatment with mean baseline measurements. Similarly, the paired Wil-

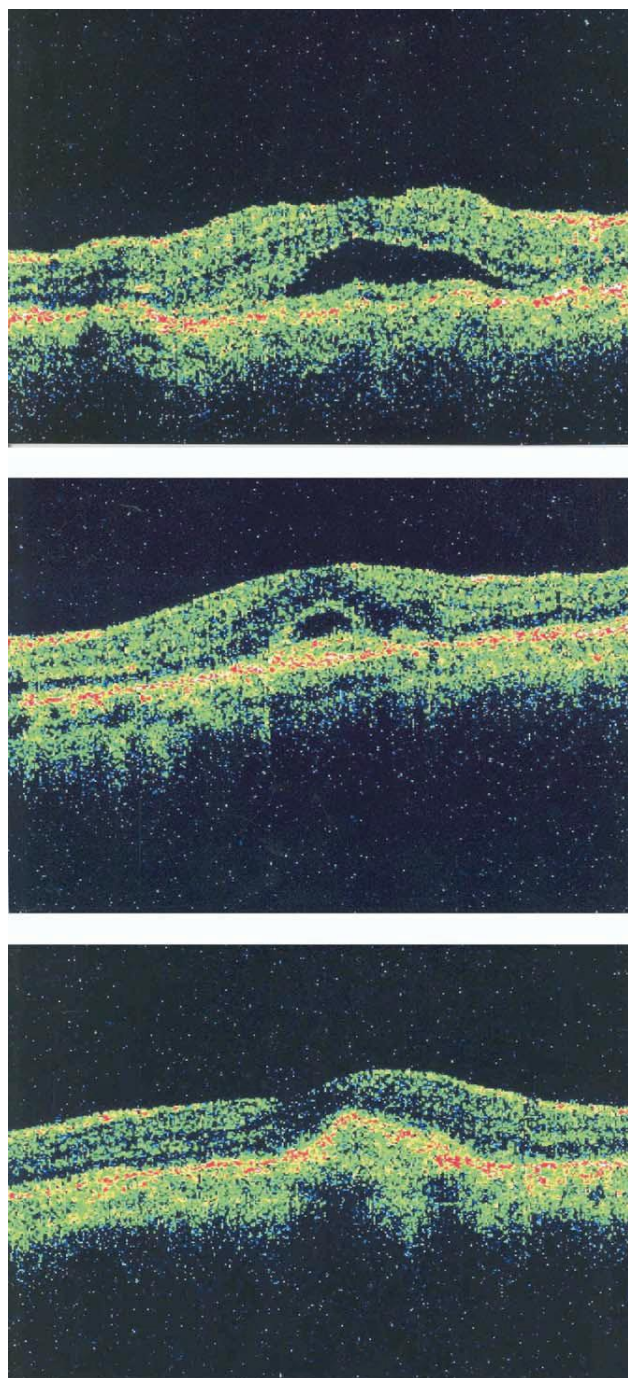


FIGURE 3. Ocular coherence tomography (OCT) scans and central retinal thickness (CRT) measurements for an eye with subfoveal choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) that had complete resolution of subretinal fluid after the second intravitreal injection of bevacizumab. (Top) Baseline CRT is 328 μm with visual acuity of 20/200. (Middle) Four weeks after the first injection, CRT is 209 μm with visual acuity of 20/80. (Bottom) Four weeks after second injection or after eight weeks total follow-up, CRT is 181 μm with visual acuity of 20/40. Follow-up OCT at 12 weeks continued to show no subretinal fluid, and visual acuity remained 20/40.

coxon signed rank test was applied to compare the median visual acuity and CRT at weeks four to 12 with median baseline values. The level of statistical significance was set at $P < .05$ with a 95% confidence interval.

RESULTS

IN AUGUST 2005, 17 EYES OF 17 PATIENTS RECEIVED INTRA-vitreal bevacizumab. There were five women and 12 men. The average age was 68.3 years with a range of 59 to 78 years. All eyes had subfoveal CNV due to AMD. Four eyes had poor response to PDT. Four eyes were not eligible for PDT because a minimally classic CNV was greater than four disk areas, and two eyes had more than 50% of the CNV covered by subretinal blood. None of these eyes had blood covering the fovea. The remainder of the patients refused PDT.

All eyes tolerated the procedure with no complications. Mean baseline BCVA was 20/252 (median 20/200) and mean CRT was 362 μm (median 350 μm). At the four-week follow-up, mean and median BCVA improved to 20/105 ($P < .001$) and 20/80 ($P = .001$), respectively. Mean and median CRT at four weeks decreased to 279 μm ($P < .001$) and 282 μm ($P < .001$), respectively. Three (18%) of 17 eyes had complete resolution of subretinal fluid and retinal pigment epithelial detachment on OCT (Figures 1 and 2).

Mean BCVA at eight weeks (four weeks after the second injection) improved to 20/79 ($P < .001$), and median BCVA was 20/50 ($P < .001$). In addition, mean CRT decreased to 231 μm ($P < .001$), and median CRT decreased to 230 μm ($P < .001$). At the eighth week of follow-up, seven (41%) of 17 eyes had total resolution of SRF and PED on OCT (Figures 3 and 4). This included the three eyes that had such a response after the first injection.

Mean and median BCVA at 12 weeks (four weeks after the third injection) stabilized at 20/76 ($P < .001$) and 20/50 ($P < .001$), respectively. Both mean and median CRT at 12 weeks decreased further to 211 μm . This was statistically better than mean baseline CRT ($P < .001$) and median baseline CRT ($P < .001$). Thirteen (76%) of 17 eyes had total resolution of SRF and PED on OCT (Figures 5 and 6). Tables 1 and 2 summarize the visual acuity and CRT data over 12 weeks.

After 12 weeks, all 17 eyes had improvement in CRT (Figure 7), and eight (47%) of 17 eyes had CRT equal to or less than 200 μm . Fifteen (88%) of 17 eyes had better BCVA at 12 weeks than baseline, whereas two eyes did not improve (Figure 8). Four (24%) of 17 eyes ended with BCVA better than 20/50. All 17 eyes had marked reduction or absence of leakage from the CNV on angiography; however, the improvement on angiography did not occur as rapidly as that noted on OCT. We did not note any ocular side effects at any stage. There was no significant rise in intraocular pressure or progression of cataract.

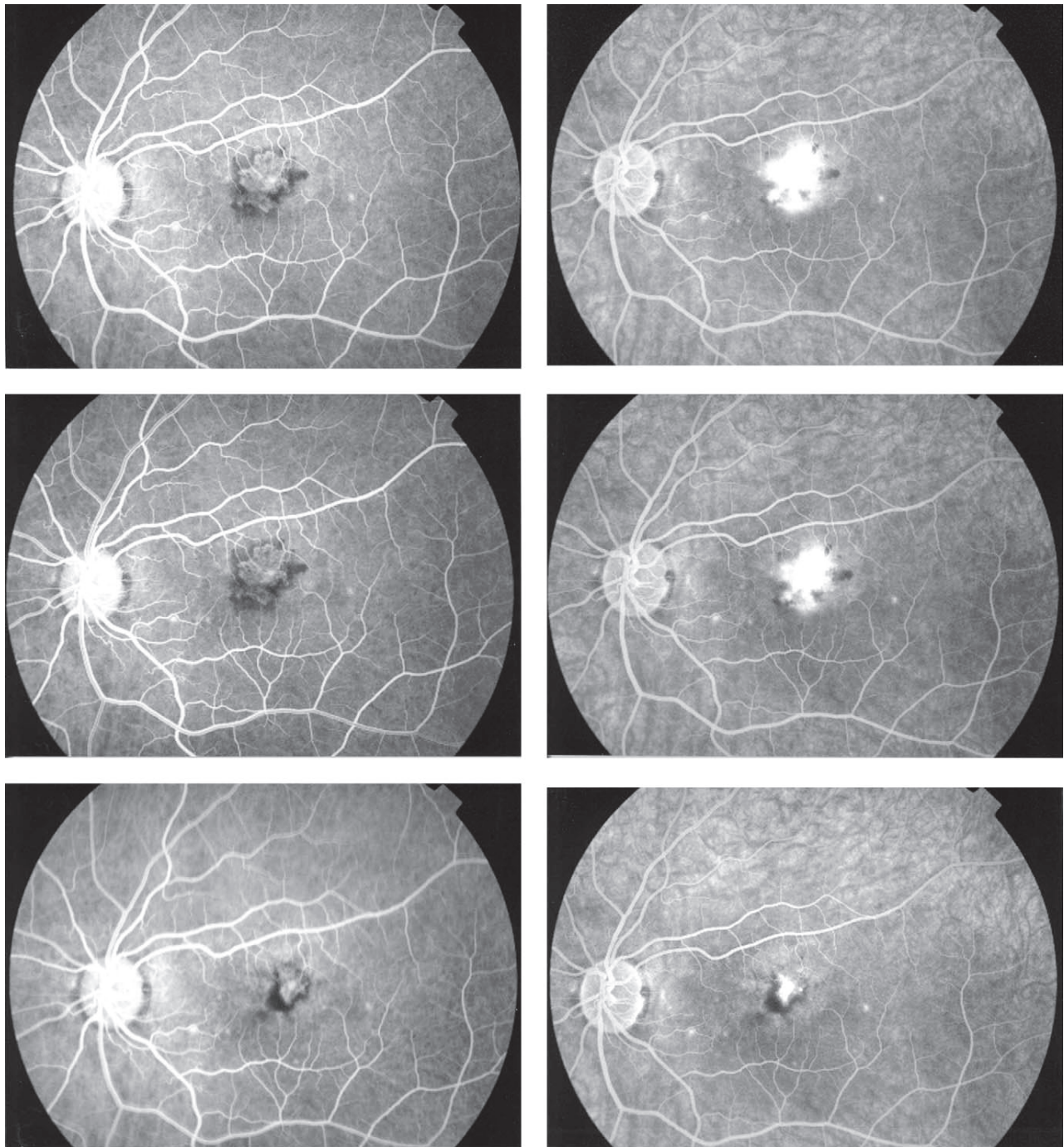


FIGURE 4. Fluorescein angiographic changes in choroidal neovascularization (CNV) for the eye in Figure 3 after two intravitreal injections of bevacizumab. Early-phase (Top left) and late-phase (Top right) angiograms at baseline show classic CNV. Four weeks after the first injection, there is no change in the early-phase (Middle left) and late-phase (Middle right) angiograms. Four weeks after the second injection or after eight weeks of follow-up, there is considerable decrease in the size of the CNV in the early phase (Bottom left) and decreased leakage in the late phase (Bottom right). Angiography at 12 weeks remained unchanged.

Mean baseline arterial blood pressure was 138/86. At no time during follow-up did the blood pressure rise noticeably above baseline. Also, no thromboembolic events were observed during the period of this study.

DISCUSSION

WE TREATED 17 EYES WITH CNV DUE TO AMD WITH INTRA-vitreal bevacizumab. After 12 weeks of follow-up, these

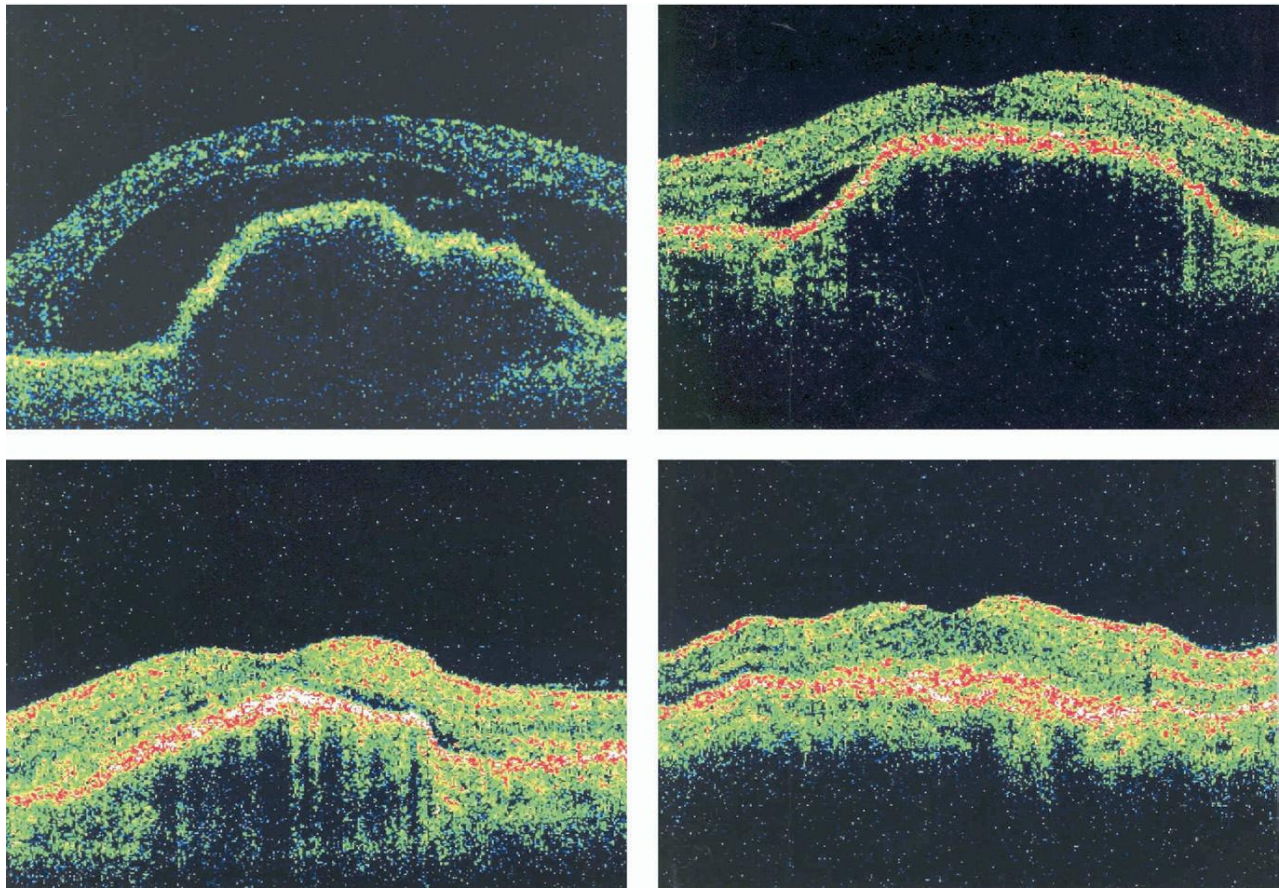


FIGURE 5. Ocular coherence tomography scans and central retinal thickness (CRT) measurements for an eye with subfoveal choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) that showed complete resolution of subretinal fluid after the third intravitreal injection of bevacizumab. (Top left) Baseline CRT is 549 μm with visual acuity of 20/200. (Top right) Four weeks after first injection, CRT is 406 μm with visual acuity still 20/200. (Bottom left) Four weeks after second injection or at eight weeks, CRT is 311 μm and visual acuity is 20/70. (Bottom right) Four weeks after third injection or at 12 weeks, CRT is 209 μm and visual acuity is 20/70.

eyes showed marked improvement in visual acuity and CRT. There were no untoward effects even after three injections using 2.5 mg. It may be that bevacizumab is less immunogenic than ranibizumab. With ranibizumab, the dose-limiting toxicity was intraocular inflammation and the maximum tolerated dose was 0.5 mg.¹⁹ Although mean CRT improved after each injection, there was no appreciable improvement in mean BCVA after the second injection. Perhaps photoreceptor damage from the CNV limited further visual improvement.

The efficacy of intravitreal bevacizumab for the treatment of CNV due to AMD raises the question about its mechanism of action. Bevacizumab inhibits all isoforms of VEGF by blocking its interaction with membrane-bound tyrosine kinase receptors VEGFR-1 and VEGFR-2.^{20,21} This would block activation of the intracellular tyrosine kinase, which would inhibit VEGF-induced cell proliferation, survival, permeability, nitric oxide production, migration, and tissue factor production.⁵ Animal studies

suggested that the bevacizumab molecule was too large to cross the retina into the subretinal space.²² However, the results from this series and the report by Rosenfeld and associates¹⁷ confirm the effect of intravitreal bevacizumab on CNV. One possibility is that this large molecule is able to cross a diseased retina more readily. Another possibility is that bevacizumab inhibits VEGF in the vitreous, the surface of the retina, or inside the retina, which may be enough to prevent further growth and leakage from the CNV. Finally, results of the animal studies may not apply to the human eye, and bevacizumab is able to cross the retina.

There are several potential adverse effects associated with the systemic use of VEGF inhibitors, such as increased risk for thromboembolic events, hypertension, epistaxis, hemoptysis, proteinuria, delayed wound healing after surgery, and impaired reproductive function.^{16,21} Visual loss in the fellow eye may occur by inhibiting VEGF, which would cause regression of the choriocapillaris.²³

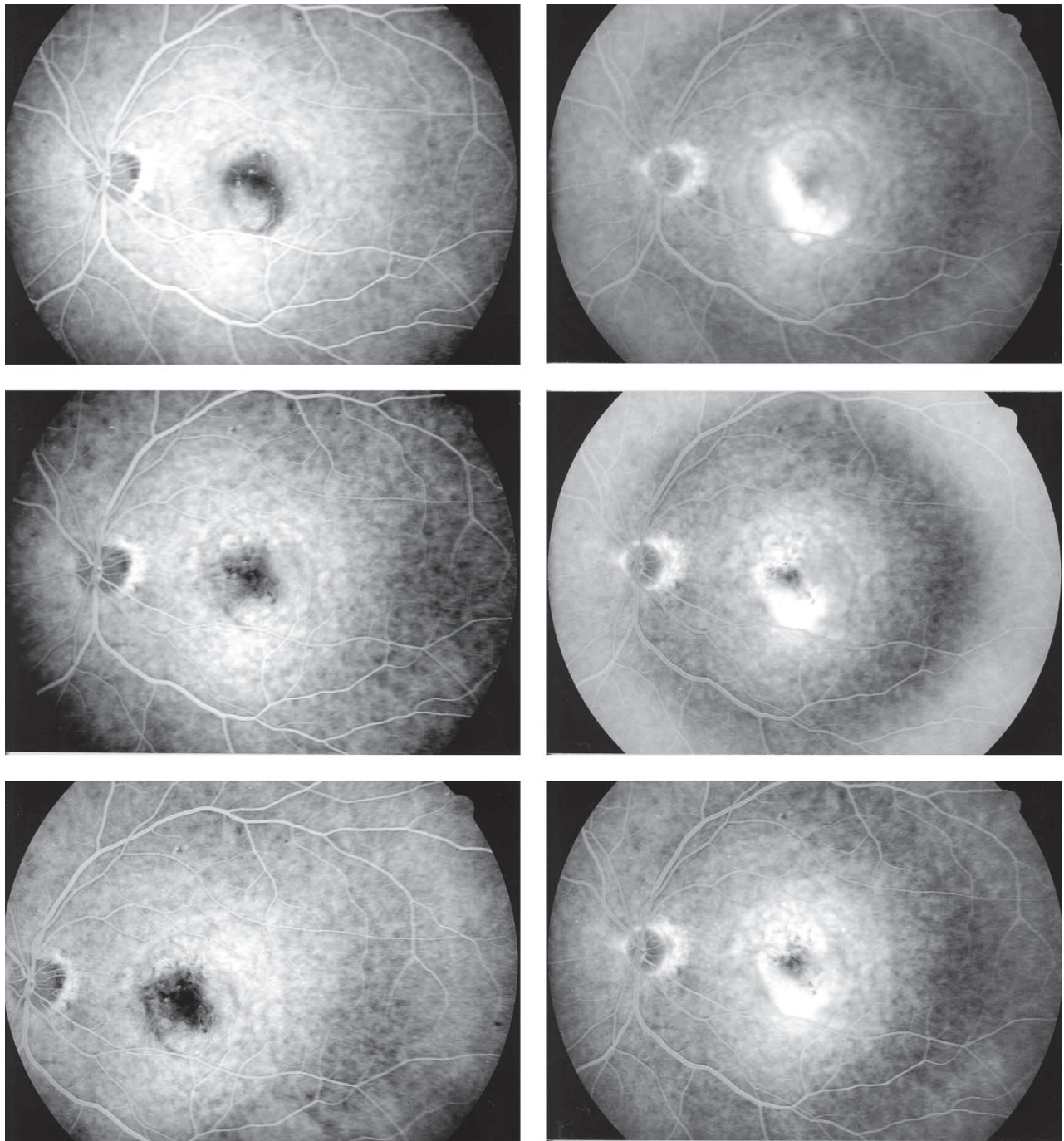


FIGURE 6. Fluorescein angiographic changes in the choroidal neovascularization (CNV) for the eye in Figure 5 after the three intravitreal injections of bevacizumab. Early-phase (Top left) and late-phase (Top right) angiograms at baseline. Early-phase (Middle left) and late-phase (Middle right) angiograms four weeks after the first injection. Early-phase (Bottom left) and late-phase (Bottom right) angiograms four weeks after the third injection or at the 12 weeks of follow-up.

Intravitreal administration of bevacizumab would help avoid these adverse events and allow a direct targeting of choroidal neovascularization by the antibody. The intravitreal route also allows for the use of a much lower dose of the agent compared with the intravenous approach (total

dose of 2.5 mg vs 5 mg/kg dose used intravenously). However, intravitreal injections pose several potential risks, including endophthalmitis, vitreous hemorrhage, and retinal detachment. Intravitreal bevacizumab itself may cause inflammation or ocular toxicity with repeated injec-

TABLE 1. Mean and Median Visual Acuity Over 12 Weeks for 17 Eyes With Choroidal Neovascularization Treated With Intravitreal Bevacizumab

Number of Eyes (n = 17)	Baseline Visual Acuity (Snellen)	Week 4 Visual Acuity (Snellen)	Week 8 Visual Acuity (Snellen)	Week 12 Visual Acuity (Snellen)
Median (P value)*	20/200	20/80 (0.001)	20/50 (<0.001)	20/50 (<0.001)
Mean (P value)†	20/252	20/105 (<0.001)	20/79 (<0.001)	20/76 (<0.001)

*Paired Wilcoxon signed rank test.

†Paired Student *t* test.

TABLE 2. Mean and Median Central Retinal Thickness Over 12 Weeks for 17 Eyes With Choroidal Neovascularization Treated With Intravitreal Bevacizumab

Number of Eyes (n = 17)	Baseline Central Retinal Thickness (μm)	Week 4 Central Retinal Thickness (μm)	Week 8 Central Retinal Thickness (μm)	Week 12 Central Retinal Thickness (μm)
Median (P value)*	350	282 (<0.001)	230 (<0.001)	211 (<0.001)
Mean (P value)†	362	279 (<0.001)	231 (<0.001)	211 (<0.001)

*Paired Wilcoxon signed rank test.

†Paired Student *t* test.

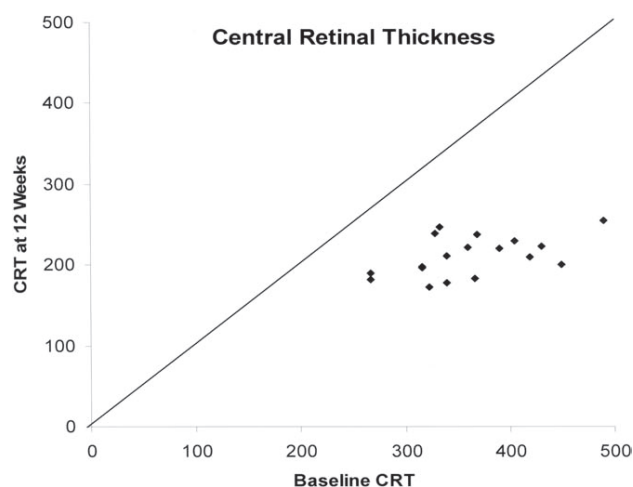


FIGURE 7. Scatter plot of baseline central retinal thickness (CRT) vs central macular thickness at 12 weeks for 17 eyes that received intravitreal bevacizumab for subfoveal choroidal neovascularization (CNV) due to age-related macular degeneration (AMD). All points below the line imply improved final CRT.

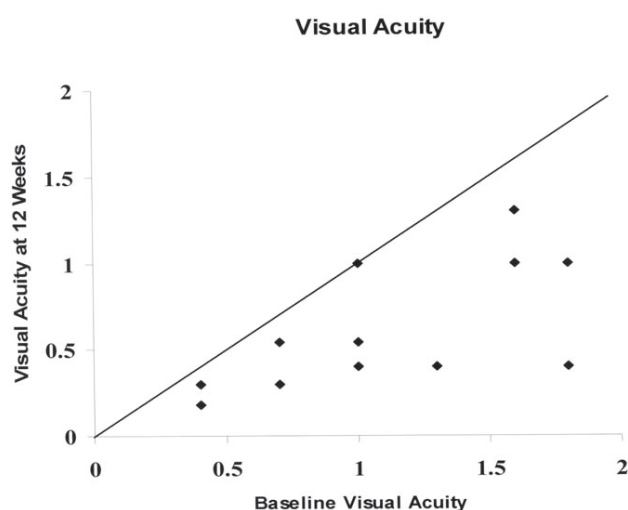


FIGURE 8. Scatter plot of baseline visual acuity vs visual acuity at 12 weeks (expressed in logMAR units) for 17 eyes that received intravitreal bevacizumab for subfoveal choroidal neovascularization (CNV) due to age-related macular degeneration (AMD). All points below the line imply improved final visual acuity.

tions. None of these side effects was observed in the 17 treated eyes.

Because of the small sample size and the short follow-up in this study, we cannot draw conclusions about the long-term efficacy and safety of intravitreal bevacizumab. Longer follow-up is necessary to determine the long-term safety of this treatment. We used 2.5 mg of bevacizumab, which is greater than that used by Rosenfeld and associates.¹⁷ Although no

dose-ranging studies were done, we assumed a higher intravitreal concentration may allow greater VEGF inhibition and a greater availability in the subretinal space. We also decided on monthly injections mainly because other anti-VEGF trials (MARINA Study Group, unpublished data, presented at American Society of Retina Specialists Annual Meeting, July 2005) utilized periodic intravitreal injections. We thought

these successive injections would lead to better VEGF inhibition, which may achieve regression of CNV in the short term, because VEGF is necessary for survival of immature blood vessels.²³ Despite the longer half-life of bevacizumab compared with ranibizumab,²⁴ bevacizumab has a lower affinity to VEGF²⁵ and is a larger molecule that may achieve lower subretinal concentrations. Therefore, monthly intravitreal injections may achieve better CNV control. Of course, other studies are necessary to determine the ideal dose, number of injections, and frequency of injections. Further randomized trials should also compare intravitreal bevacizumab with other available anti-VEGF agents, such as pegaptanib sodium and ranibizumab.

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