Systemic Bevacizumab (Avastin) Therapy for Neovascular Age-Related Macular Degeneration

Twelve-Week Results of an Uncontrolled Open-Label Clinical Study

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Purpose: To evaluate the short-term safety of systemic bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA) and its effects on visual acuity (VA) and subfoveal choroidal neovascularization (CNV) in patients with neovascular age-related macular degeneration (AMD).

Design: Open-label, single-center, uncontrolled clinical study.

Participants: Age-related macular degeneration patients with subfoveal CNV (N = 9) and best-corrected VA letter scores of 70 to 20 (approximate Snellen equivalent, 20/40–20/400).

Methods: Patients were treated at baseline with an infusion of bevacizumab (5 mg/kg), followed by 1 or 2 additional doses given at 2-week intervals. Safety assessments were performed at all visits. Ophthalmologic evaluations included protocol VA measurements and ocular examinations, along with optical coherence tomography (OCT) imaging, fluorescein angiography, and indocyanine green angiography.

Main Outcome Measurements: Safety assessments were performed, along with assessments of changes from baseline in VA scores, OCT measurements, and angiographic lesion characteristics.

Results: There were no serious ocular or systemic adverse events identified. By 6 weeks, the only adverse event identified was a mild elevation of systolic blood pressure (BP) (+12 mmHg; $P = 0.035$), and this elevation was controlled by either changing or initiating antihypertensive medication. By 12 weeks, the elevation of systolic BP was no longer significant ($P = 0.51$). In the study eyes, significant increases in VA were evident within 1 week of treatment, and by 12 weeks, the median and mean VA letter scores increased by 8 letters ($P = 0.011$) and 12 letters ($P = 0.008$), respectively. The median and mean central retinal thickness measurements decreased by 157 μm ($P = 0.008$) and 177 μm ($P = 0.001$), respectively. In the fellow eyes at 12 weeks, the median and mean VA letter scores increased by 27 letters ($P = 0.018$) and 16 letters ($P = 0.012$), and the median and mean central retinal thickness measurements decreased by 59 μm ($P = 0.028$) and 92 μm ($P = 0.06$). In all study eyes, angiography revealed a marked reduction or an absence of leakage from CNV.

Conclusion: Overall, bevacizumab therapy was well tolerated, with an improvement in VA, OCT, and angiographic outcomes. Although these preliminary results are promising, a randomized controlled clinical trial is necessary before concluding that systemic bevacizumab therapy is safe and effective for patients with neovascular AMD. *Ophthalmology 2005;112:1035–1047 © 2005 by the American Academy of Ophthalmology.*

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Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss among the elderly in North America and Europe, and macular neovascularization in these patients is the most common cause of severe vision loss.[1–4] Macular neovascularization in AMD usually arises from the choroidal circulation under the retina and is commonly known as choroidal neovascularization (CNV), whereas the term *retinal angiomatous proliferation* (RAP) is used when describing a subset of lesions that have a significant intraretinal component of neovascularization.[5,6] Historically, the term *choroidal neovascularization* has been used to designate all forms of macular neovascularization secondary to AMD. These neovascular lesions can be classified using both fluorescein angiography and indocyanine green angiography,[7,8] and lesion type classification is important in determining when to offer treatment. The most widely accepted classification scheme uses fluorescein angiography, and the major fluorescein angiographic subtypes of neovascularization are known as predominantly classic, minimally classic, and occult with no classic (occult-only) CNV. This classification scheme serves as the basis for some current treatments, which include laser photocoagulation and verteporfin photodynamic therapy (PDT).

Both laser photocoagulation and PDT target CNV for destruction. Photodynamic therapy is one current treatment for neovascular AMD patients with lesions involving the geometric center of the fovea, known as subfoveal lesions.[9–12] Although PDT is superior to placebos for preventing moderate vision loss in patients with predominantly classic lesions and may be superior to placebos for patients with relatively small minimally classic and occult-only lesions, there is little chance of vision improvement in these patients.

Several promising pharmacologic strategies have been developed to improve treatment outcomes for neovascular AMD patients. One approach is to combine PDT with an intraocular injection of triamcinolone acetonide.[13,14] Another strategy is to block the angiogenic factors that may be responsible for neovascularization in AMD. Several angiogenic factors have been identified as likely stimuli for neovascularization in AMD.[15] Of all these angiogenic factors, vascular endothelial growth factor (VEGF) is implicated as the major stimulus responsible for neovascularization in AMD.[16–20] In addition to its ability to promote vascular endothelial cell growth and survival, VEGF has been shown to increase vascular permeability and promote the recruitment of leukocytes.[21] All the properties that have been attributed to VEGF are likely to be important in promoting the growth and leakage of CNV.

One possible strategy to prevent and treat CNV is to inhibit VEGF. In an animal model of laser-induced CNV, intravitreal injections of an anti-VEGF drug known as ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA) inhibited the formation of CNV.[22] In human phase I/II clinical trials, promising results were reported after intravitreal injections of the anti-VEGF drugs pegaptanib (Macugen, Eyetech Pharmaceuticals, New York, NY)[23–25] and ranibizumab (unpublished data).[26] Once injected into the eye, the proposed mechanism of action for both pegaptanib and ranibizumab involves the penetration of these drugs through the retina, followed by competitive inhibition of VEGF in the extracellular space.

Positive results from the phase III clinical trials with pegaptanib sodium were recently published,[27] and pegaptanib was approved by the Food and Drug Administration (FDA) for the treatment of neovascular AMD on December 17, 2004. At 1 year, vision loss was significantly slowed in neovascular AMD patients receiving pegaptanib therapy compared with patients receiving a sham intraocular injection. By week 6 of the trials, the difference in vision loss between these 2 groups was apparent. Although most patients continued to lose vision during the first year of the trial, there were some patients (6%) who experienced a significant 3-line improvement in visual acuity (VA).

Another method for delivering anti-VEGF therapy to the eye in neovascular AMD patients would be to use systemic therapy rather than an intraocular injection. In animal experiments, systemic anti-VEGF therapy has been shown to inhibit the formation of CNV.[28,29] One systemic drug that has been studied in animals and is mechanistically related to pegaptanib and ranibizumab is the fusion protein known as the VEGF-Trap.[30,31] This drug combines the extracellular domains of the 2 VEGF receptors, known as VEGFR-1 and VEGFR-2, with the Fc portion of an immunoglobulin G1 to create an antibody-like molecule that competitively binds VEGF with high affinity ($K_d \approx 1.0$ pmol/l). Systemic VEGF-Trap is currently in phase I/II clinical trials for the treatment of neovascular AMD.

Currently, a full-length recombinant humanized monoclonal antibody directed against VEGF known as bevacizumab (Avastin, Genentech, Inc.) is approved by the FDA for the treatment of metastatic colorectal cancer.[32–36] The antiangiogenic properties of bevacizumab have been studied in cancer patients, but never in animal models or humans with CNV. However, fluorescein-conjugated bevacizumab was shown to leak from laser-induced CNV after systemic administration to a cynomolgus monkey.[37] This observation

Table 1. Major Inclusion/Exclusion Criteria

Inclusion
• Age > 50 yrs
• Primary or recurrent subfoveal CNV due to AMD
• Central 1-mm retinal thickness (optical coherence tomography) ≥ 300 μm
• Ineligible for verteporfin PDT or patient refuses PDT
• Best-corrected visual acuity, using ETDRS charts, of 20/40–20/400
• Evidence of recent disease progression, including the loss of at least 1 line of visual acuity or macular hemorrhage within the previous 12 wks
Exclusion
• Uncontrolled hypertension
• Coagulation abnormalities as determined by measurement of PT/PTT, bleeding time, and platelet levels
• Renal dysfunction
• History of thromboembolic events, including stroke, transient ischemic attacks, and myocardial infarction
• Ongoing anticoagulation therapy, excluding aspirin
• Need for surgery within 3 mos of enrollment

AMD = age-related macular degeneration; CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study; PDT = photodynamic therapy; PT/PTT = prothrombin time/partial thromboplastin time.

Table 3. Study Eyes: Change in Visual Acuity through 12 Weeks

Patients' Study Eyes (N = 9)	Baseline Visual Acuity Letters (Snellen Equivalent)	Week 1 Visual Acuity Letters (Snellen Equivalent)	Week 6 Visual Acuity Letters (Snellen Equivalent)	Week 12 Visual Acuity Letters (Snellen Equivalent)	Change in Visual Acuity Letter Scores from Baseline to Week 12
Median (*P* value)*	56 ($20/80^{+1}$)	62 ($20/63^{+2}$) (0.018)	65 (20/50) (0.007)	64 ($20/50^{-1}$) (0.011)	8 (1.6 lines)
Mean (*P* value)†	54 ($20/80^{-1}$)	60 (20/63) (0.011)	67 ($20/50^{+2}$) (0.005)	66 ($20/50^{+1}$) (0.008)	12 (2.4 lines)

*Paired Wilcoxon signed rank test.
†Paired Student's *t* test.

suggested to us that systemic bevacizumab could leak from CNV in AMD patients and competitively inhibit extracellular VEGF.

At the time that we initiated an open-label prospective clinical study, the Systemic Avastin for Neovascular AMD (SANA) Study, we proposed that systemic bevacizumab could leak from CNV and bind extracellular VEGF, that inhibition of extracellular VEGF could improve VA outcomes based on the promising results from early-phase studies with intravitreal anti-VEGF drugs, and that bevacizumab could be used for this off-label indication in neovascular AMD patients destined to become legally blind for whom no approved therapy existed. This article reports on the first 9 patients enrolled in this study through the first 12 weeks of follow-up.

Patients and Methods

Approval for the SANA Study was obtained from the institutional review board/ethics committee at the University of Miami School of Medicine. The SANA Study will observe patients for at least 1 year after enrollment. Informed consent was obtained from all patients before determination of full eligibility (Table 1), and this research was compliant with the Health Insurance Portability and Accountability Act of 1996. At the start of this study, eligible eyes were designated study eyes, and if both eyes were eligible, then the enrolling investigator assigned one eye as the study eye. All treatment decisions were made based on the findings in the study eye. The nonstudy eye was designated the fellow eye. Only AMD patients with eyes containing subfoveal CNV ineligible for verteporfin PDT or patients who refused PDT could be enrolled. All study eyes demonstrated recent disease progression, as defined by documented vision loss (>1 line), a growth in their CNV of >10%, or new-onset macular hemorrhage within the previous 12 weeks. Patients with uncontrolled hypertension (systolic blood pressure [BP] of ≥150 mmHg or diastolic BP of ≥90 mmHg); history of a thromboembolic event, including myocardial infarction or cerebral vascular accident; renal abnormalities; recent or planned surgery; or coagulation abnormalities, including current anticoagulation medication other than aspirin, were excluded from the study.

All patients underwent a full physical examination by an internal medicine specialist at baseline. Baseline laboratory testing included an electrocardiogram, complete blood count, chemistry panel, prothrombin time, partial thromboplastin time, bleeding time, and urinalysis. Laboratory testing was repeated every 3 months. Blood pressure was measured at least twice during each visit, and the study was later amended to include 3 separate BP measurements at each visit according to standard procedures.[38] In addition, when bevacizumab was infused, BP was measured before, during, and after each infusion. The systolic and diastolic BP measurements were averaged for each visit. Medical management of BP was performed by a University of Miami board-certified internist at the Bascom Palmer Eye Institute according to the recommendations of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[39,40]

Best-corrected VA (BCVA) was determined using a standard Early Treatment Diabetic Retinopathy Study VA assessment procedure at 2 m, as previously described (5 letters = 1 line).[9] All Early Treatment Diabetic Retinopathy Study vision examiners were unmasked to treatment and previously certified to participate in FDA-approved clinical trials at the Bascom Palmer Eye Institute. Baseline VA letter scores had to be no better than 70 letters and no worse than 20 letters using the Early Treatment Diabetic Retinopathy Study chart (Snellen equivalent of 20/40–20/400).

Baseline 1-mm central retinal thickness was measured by optical coherence tomography (Stratus OCT, Carl Zeiss Meditec, Dublin, CA) using 6-diagonal fast and slow 6-mm scans. For enrollment, all study eyes were required to have a central thickness of at least 300 μm as determined using the Stratus OCT fast macular scan, with all retinal boundaries appropriately identified by the FDA-validated internal algorithm.

At baseline and at each visit, patients underwent VA testing, ophthalmoscopic examination, OCT imaging, and fundus photography. Fluorescein angiography was performed at baseline and every 4 weeks. Early-phase fluorescein angiographic images were usually selected between 20 and 25 seconds, mid-phase images between 60 and 90 seconds, and late-phase images between 5 and 10 minutes. Indocyanine green angiography was performed at baseline and every 12 weeks. Early-phase indocyanine green angiographic images were selected at 5 minutes after dye infusion, and late-phase images were selected at 30 minutes. All ophthalmic photographers and the only OCT technician involved in this study were unmasked to treatment and previously certified to participate in FDA-approved clinical trials at the Bascom Palmer Eye Institute.

Once the study consent form was signed, patients underwent a baseline screening evaluation, and the drug was infused if all entry criteria were fulfilled. Bevacizumab was infused at the dose of 5 mg/kg, the same dose currently approved by the FDA for the treatment of metastatic colorectal cancer patients. Three initial infusions were planned to be given at 2-week intervals, the same dosing interval approved by the FDA. The first infusion was given over 90 minutes. If no adverse events were observed, then the second dose was infused over 60 minutes, and the third dose over 45 minutes. If the central retinal thickness as measured by OCT was reduced by >50% at the time of the third dose or an adverse

Table 4. Study Eyes: Change in Central Retinal Thickness through 12 Weeks

Patients' Study Eyes (N = 9)	Baseline Central Retinal Thickness (μm)	Week 1 Central Retinal Thickness (μm)	Week 6 Central Retinal Thickness (μm)	Week 12 Central Retinal Thickness (μm)	Decrease in Central Retinal Thickness (μm) from Baseline to Week 12
Median (*P* value)*	400	306 (0.008)	248 (0.008)	243 (0.008)	157
Mean (*P* value)†	417	287 (0.001)	238 (0.001)	240 (0.001)	177

*Paired Wilcoxon signed rank test.
†Paired Student's *t* test.

event was observed such as elevated BP, the treating physician could withhold the dose.

During the first 6 weeks of the study, patients were evaluated every week. From week 6 through week 12, patients were evaluated every 2 weeks. Once the treatment was stopped after the second or third dose, additional therapy was possible if any of the following criteria were fulfilled: (1) a VA decrease of at least 5 letters at 2 sequential visits within 2 weeks, and this vision decrease associated with increased leakage from CNV, as assessed by fluorescein angiography or OCT (if the decrease in vision was not associated with leakage, then no additional drug therapy would be offered); (2) an increase in OCT central retinal thickness of >100 μm; (3) a new macular hemorrhage; and (4) a new area of classic CNV. If additional drug therapy was performed, then the reinfusion protocol was the same as described at baseline.

The outcome measurements in the SANA Study were assessed for the patient as a whole and for both the study eyes and the nonstudy fellow eyes. This study was not powered to identify frequent serious adverse events even with rates as high as 10%. Rather, this study was initiated as an exploratory investigation of a new systemic therapy for neovascular AMD to determine if the potential benefits warranted further investigation to determine the true underlying risks of this therapy in neovascular AMD patients compared with cancer patients. Safety was assessed by evaluating concomitant medications, review of systems, adverse events, vital signs, laboratory tests, BCVA, dilated ophthalmoscopic examinations, color fundus photographs, fluorescein angiograms, indocyanine green angiograms, and OCT images. Ocular outcome measurements included changes from baseline in VA and the proportion of patients gaining or losing 5 letters (1 line), 15 letters (3 lines), or 30 letters (6 lines) of BCVA from baseline. Additional outcomes included changes from baseline in OCT central retinal thickness measurements and the correlation between the change in VA and the change in central retinal thickness measurements. Assessment of neovascular lesions included changes in leakage from CNV and appearance of lesions as determined by fluorescein angiography, indocyanine green angiography, and fundus photography.

Data were statistically analyzed using the paired Student's *t* test for changes in mean BP measurements, VA letter scores, and central retinal thickness measurements at weeks 1 through 12 compared with mean baseline values. Median measurements at weeks 1 through 12 were compared with median baseline values using the paired Wilcoxon signed rank test. Statistical significance was defined as $P<0.05$. The Pearson correlation coefficient (r) was computed to determine the strength of the relationship between the improvement of VA and reduction of the central retinal thickness measurements.

Results

Baseline Characteristics

A total of 15 patients were initially screened, and 6 patients were excluded from the study for the following reasons: 4 had vision better than 20/40, 1 had uncontrolled hypertension, and 1 had a history of ischemic heart disease. The first 9 patients enrolled in the study had a mean age of 78 years and a median age of 80 years (range, 71–89), with 8 women and 1 man enrolled. All 9 patients completed the 10 visits scheduled for the first 12 weeks of the study. The types of subfoveal neovascular lesions present in the study eyes and fellow eyes are described in Table 2 (available at http://aaojournal.org), along with the number of prior treatments with PDT. The baseline median and mean VAs and central retinal thickness measurements for the study eyes are shown in Tables 3 and 4. At baseline, study eye median VA was 56 letters ($20/80^{+1}$), and the mean VA was 54 letters ($20/80^{-1}$), with a range of 34 ($20/200^{-1}$) to 65 (20/50) letters. Baseline median and mean 1-mm central retinal thickness measurements were 400 μm and 417 μm, respectively. The fellow eye baseline median and mean VAs and central retinal thickness measurements are shown in Tables 5 and 6 (available at http://aaojournal.org). Median VA in the fellow eye was 30 letters (20/250), with a mean of 40 (20/160), ranging from 12 ($20/640^{+2}$) to 84 ($20/20^{-1}$) letters. In the fellow eyes, accurate central retinal thickness measurements could be obtained in only 6 of the 9 eyes. In 1 fellow eye (patient 3), a dense cataract prevented visualization of the fundus on examination, and an OCT image of the macula could not be obtained. In the other 2 fellow eyes (patients 4 and 6), poor VA and poor cooperation resulted in nonreproducible OCT scans, and even when images were obtained, the complex macular contour of the disciform scar resulted in boundary detection artifacts that arise when the Stratus OCT algorithm fails to identify accurately the anatomic boundaries of the retina and retinal pigment epithelium (RPE) so that the retinal thickness measurements are unreliable. These 3 fellow eyes were not included in any calculations involving changes from baseline in central retinal thickness measurements.

At baseline, 3 of the 9 patients enrolled into the study were taking BP medications (Table 7). Of the remaining 6 patients at baseline, 1 was diagnosed with stage 1 hypertension (systolic BP of 140–159 mmHg or diastolic BP of 90–99 mmHg), and 4 were diagnosed with prehypertension (systolic BP of 120–139 mmHg or diastolic BP of 80–89 mmHg).

Safety

No serious ocular or systemic adverse events were reported through week 12. No vision loss of >1 letter was observed in

Table 7. Change in Mean Blood Pressure (BP) through 12 Weeks

Patient	Baseline BP,* Systolic	Baseline BP,* Diastolic	Week 6 BP,† Systolic	Week 6 BP,† Diastolic	Week 12 BP,† Systolic	Week 12 BP,† Diastolic
Median (*P* value)‡	129	77	141 (0.035)	80 (0.58)	130 (0.51)	80 (0.58)
Mean (*P* value)§	129	75	141 (0.026)	76 (0.51)	135 (0.37)	77 (0.45)

*Three of the 9 patients were on hypertension medication at baseline.
†By week 6, 7 of the 9 patients were on medication, and no medications were changed or initiated after week 6 through week 12.
‡Paired Wilcoxon signed rank test.
§Paired Student's *t* test.

either the study eyes or the fellow eyes. Hypertension was the only adverse event identified. Table 7 shows the average systolic and diastolic BPs at baseline, week 6, and week 12 for all patients. During the study, all 3 patients who were on medication at baseline required adjustment of their medications to control hypertension. The patient who had stage 1 hypertension at baseline required medication at week 5 of the study. One of the patients with prehypertension required medication at week 3, and the 1 patient with normal baseline BP required medication at week 4. Overall, a total of 7 patients received medication during the first 6 weeks of the study. By week 6, there was a statistically significant increase in the median and mean systolic BPs of 12 mmHg (median, $P = 0.035$; mean, $P = 0.026$), but no significant change in diastolic BP (Table 7). This mild but significant elevation in the mean and median systolic BPs to stage 1 hypertension by week 6 was not apparent by week 12, and no additional adjustments to medications after week 6 were necessary in any of the patients. This transient mild increase in hypertension is considered a drug-related adverse event. All laboratory testing through 12 weeks was found to be unchanged compared with baseline values.

Study Eyes: Visual Acuity and Central Retinal Thickness Outcomes

One week after the initial bevacizumab infusion, statistically significant changes in VA letter scores and central retinal thickness measurements were observed, and these significant changes continued through week 12 (Tables 3, 4). By 1 week, both median and mean VA letter scores in the study eyes increased to 62 letters ($20/63^{+2}$, +6 letters, $P = 0.018$) and 60 letters (20/63, +6 letters, $P = 0.011$), respectively. The median and mean 1-mm central retinal thickness measurements decreased significantly to 306 μm (-94 μm, $P = 0.008$) and 287 μm (-130 μm, $P = 0.001$), respectively. During the next 11 weeks, additional improvement in VA and central retinal thickness measurements was observed (Figs 1, 2). By week 6, median and mean VA letter scores had increased to 65 letters (20/50, +9 letters, $P = 0.007$) and 67 letters ($20/50^{+2}$, +13 letters, $P = 0.005$), respectively, with a reduction in median and mean central retinal thickness measurements (-152 μm, $P = 0.008$; -179 μm, $P = 0.001$) (Tables 3, 4). By week 12, the median and mean VA letter scores had stabilized at 64 letters ($20/50^{-1}$, +8 letters, $P = 0.011$) and 66 letters ($20/50^{+1}$, +12 letters, $P = 0.008$), with a stable reduction in median and mean central retinal thickness measurements (-157 μm, $P = 0.008$; -177 μm, $P = 0.001$) (Tables 3, 4). At week 12, there were 3 eyes (33%) with at least 3 lines of VA improvement and 8 eyes (89%) with at least 1 line of improvement (Table 8). The remaining eye was stable, with a loss of 1 letter due to evidence of recurrent leakage from CNV (patient 7).

Fellow Eyes: Visual Acuity and Central Retinal Thickness Outcomes

One week after the initial bevacizumab infusion, there was no significant change in the median and mean VA letter scores, but there was a significant decrease in the median central retinal thickness measurement (Tables 5, 6 [available at http://aaojournal.org]). Over the next 11 weeks, the median and mean VA letter scores improved and the central retinal thickness measurements decreased (Figs 3, 4 [available at http://aaojournal.org]). By week 12, median and mean VA letter scores had increased significantly to 57 letters ($20/80^{+2}$, +27 letters, $P = 0.018$) and 56 letters ($20/80^{+1}$, +16 letters, $P = 0.012$), respectively, with a significant decrease in the median central retinal thickness measurement (-59 μm, $P = 0.028$) and a decrease in the mean central retinal thickness (-92 μm, $P = 0.06$) of borderline significance (Tables 5, 6). At week 12, there were 4 eyes (50%) with at least 3 lines of VA improvement and 6 eyes (75%) with at least 1 line of improvement (Table 8). The remaining 2 eyes were stable (patients 1 and 8; Table 8). Fellow eye calculations for median and mean VA did not include the data from patient 3, who experienced dramatic improvement in vision after cataract surgery. Fellow eye calculations for median and mean central retinal thickness measurements did not include data from patients 3, 4, and 6 due to their unreliable baseline OCT images.

Correlation between Change in Visual Acuity and Change in Central Retinal Thickness Measurements

The Pearson correlation coefficient (r) was calculated for both study eyes and fellow eyes to assess the relationship between change in VA and change in central retinal thickness measurements. Of the 18 potential eyes, 9 of the study eyes and 6 of the fellow eyes were included in this calculation. The 3 fellow eyes excluded from the correlation belonged to patients 3, 4, and 6. The fellow eye of patient 3 was excluded because the increase in VA was attributed to cataract surgery and the baseline central retinal thickness measurement could not be obtained due to the presence of the cataract. Fellow eye OCT values from patients 4 and 6 were excluded due to unreliable baseline central retinal thickness measurements. For the 15 eyes evaluated, there was a statistically significant correlation between the decrease in central retinal thickness and the increase in VA by week 12, as shown in Figure 5 ($r = 0.7$, $P = 0.004$). When evaluated separately, the correlation for the study eyes was good and trending towards significance, but not statistically significant ($r = 0.61$, $P = 0.08$), whereas the correlation for the fellow eyes was statistically significant ($r = 0.93$, $P = 0.006$).

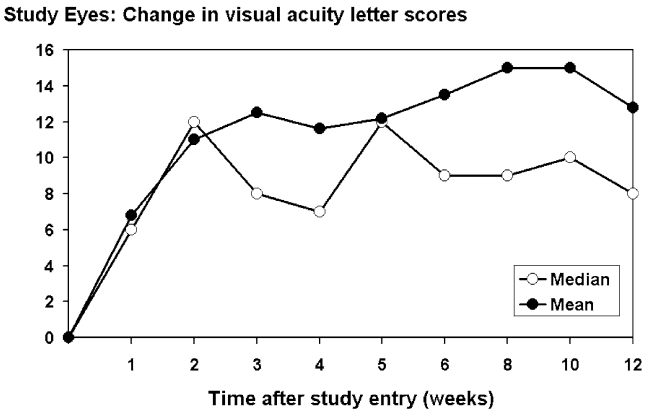

Figure 1. Study eyes: median and mean change in visual acuity letter scores through 12 weeks (5 letters = 1 line).

Case Reports*

Patient 1 (Figures 6–8)

An 89-year-old woman was complaining of vision loss in her left eye (study eye) after a single treatment with PDT. Three months after PDT, she was diagnosed with a large submacular hemorrhage in association with leakage from subfoveal occult CNV (study eye; Figs 6A, 7A, 8A). The lesion in the right eye (fellow eye) was diagnosed as a fibrotic scar with an area of active CNV in the temporal macula. At baseline, BCVAs were $20/80^{+1}$ in the study eye and 20/500 in the fellow eye. Central retinal thicknesses on OCT were 449 μm in the study eye (Fig 8A) and 171 μm in the fellow eye. The patient received 3 IV bevacizumab infusions at 2-week intervals. Visual acuity remained stable in the study eye (left eye) at week 1 and improved to $20/63^{+1}$ by week 12. The fellow eye vision was stable at 20/500 through week 12. In the study eye, central retinal thickness decreased by 208 μm at week 1 and by 256 μm at week 12 (Fig 8B–E). In the fellow eye, the central retinal thickness decreased by 36 μm at week 12. Fluorescein angiography showed an absence of leakage from both eyes by week 4, and the large submacular hemorrhage in the study eye resolved by week 12 (Fig 6B, C). With resolution of the hemorrhage in the study eye, an underlying tear of the RPE became apparent; this tear was most likely the cause for the hemorrhage before enrollment. Indocyanine green angiography showed subfoveal plaques in the late frames from both eyes that became less hyperfluorescent and better demarcated by week 12 (Fig 7). In the fellow eye at week 12, fluorescein angiography demonstrated resolution of leakage from CNV and resolution of the hemorrhage along the inferotemporal border of the central macular scar. Indocyanine green angiography showed resolution of the early focal hyperfluorescence that was associated with this hemorrhage at baseline.

*For the case reports of patients 8 and 9, see "Appendix" at http://aaojournal.org.

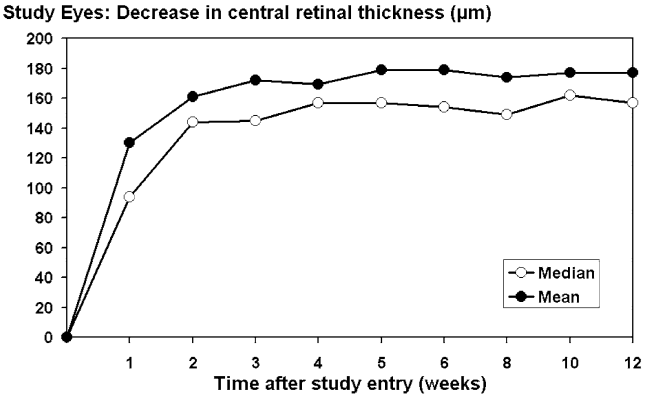

Figure 2. Study eyes: median and mean change in the central 1-mm retinal thickness of the macula as measured by optical coherence tomography through 12 weeks.

Table 8. Frequency Distribution of Changes in Visual Acuity from Baseline

Change in Visual Acuity from Baseline to Week 12	Patients [N (%)]	
	Study Eye (*N* = 9)	*Fellow Eye** (*N* = 8)†
≥6-line increase	1 (11)	2 (25)
≥3-line to <6-line increase	2 (22)	2 (25)
≥1-line to <3-line increase	5 (55)	2 (25)
No change (within 1 line)	1 (11)	2 (25)
≥1-line decrease	0	0

*Of the 9 eyes, 8 had evidence of active or prior choroidal neovascularization.
†One patient (patient 3) was not included, due to the significant improvement (+37 letters, +7 lines) after cataract surgery.

Patient 2 (Figures 9–11)

An 80-year-old woman with recent vision loss in both eyes was diagnosed with subfoveal minimally classic CNV in the right eye (study eye; Figs 9–11) and recurrent CNV along the inferior edge of a laser photocoagulation scar in the left eye. The lesion in the study eye was consistent with the diagnosis of RAP based on the characteristic OCT findings of cystic maculopathy associated with a retinal pigment epithelial detachment and indocyanine green angiographic findings of focal early hyperfluorescence (hot spots) (Figs 10A, 11A). At baseline, BCVAs were $20/80^{-1}$ in her study eye and $20/50^{+2}$ in her fellow eye. Central retinal thicknesses on OCT were 539 μm in the study eye (Fig 11A) and 245 μm in the fellow eye. The patient received 3 IV infusions of bevacizumab at 2-week intervals.

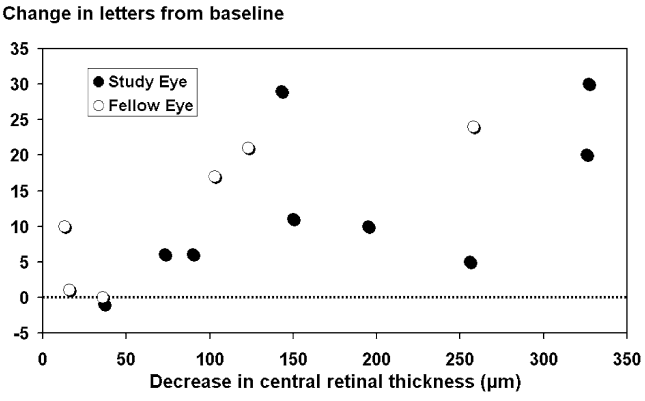

Figure 5. Study eyes and fellow eyes: correlation between the decrease in central retinal thickness and the increase in the visual acuity letter score through 12 weeks (all eyes, $r = 0.70$, $P = 0.004$; study eyes, $r = 0.61$, $P = 0.08$; fellow eyes, $r = 0.93$, $P = 0.006$).

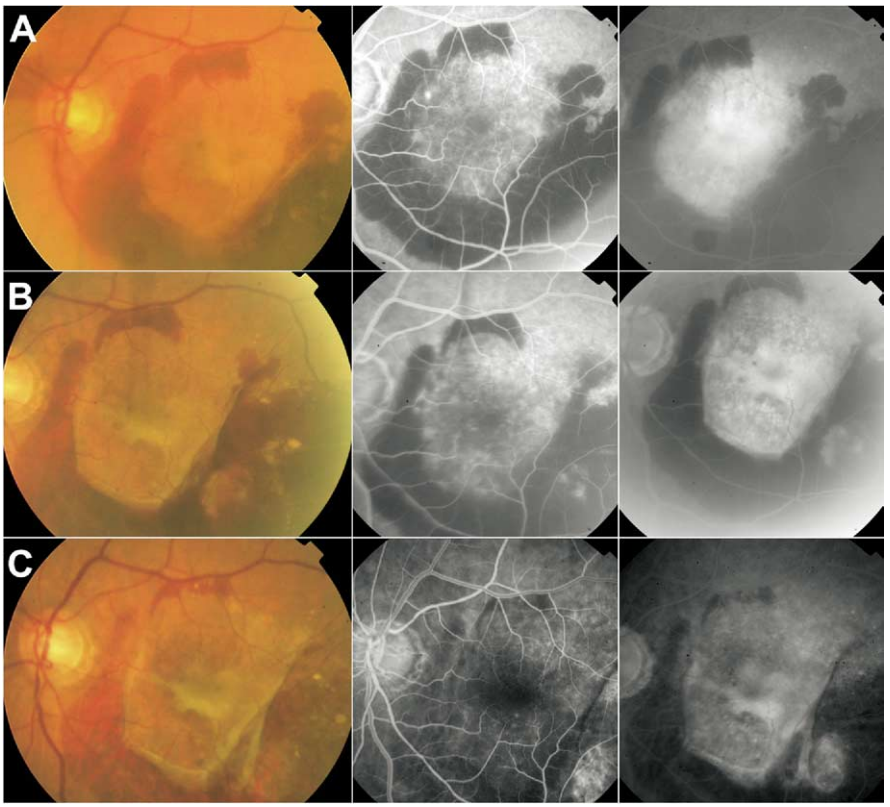

Figure 6. Patient 1, study eye: color fundus photographs with early- and late-phase fluorescein angiographic images at (**A**) baseline, (**B**) week 4, and (**C**) week 12.

Visual acuity improved in the study eye to $20/40^{+2}$ at week 1, $20/20^{-1}$ at week 6, and $20/20^{-1}$ at week 12. Fellow eye vision was stable at week 1 and then improved to $20/32^{+2}$ by week 12. In the study eye, the central retinal thickness decreased by 179 μm at week 1 and by 327 μm at week 12 (Fig 11B–E), with resolution of the pigment epithelial detachment and cystic maculopathy observed at baseline. There was little change in the fellow eye central retinal thickness by week 12, although the foveal contour improved. Fluorescein angiography showed an absence of leakage from CNV in both eyes by week 4, and the small hemorrhage along the inferior edge of the laser scar in the fellow eye resolved by week 12. At week 12, indocyanine green

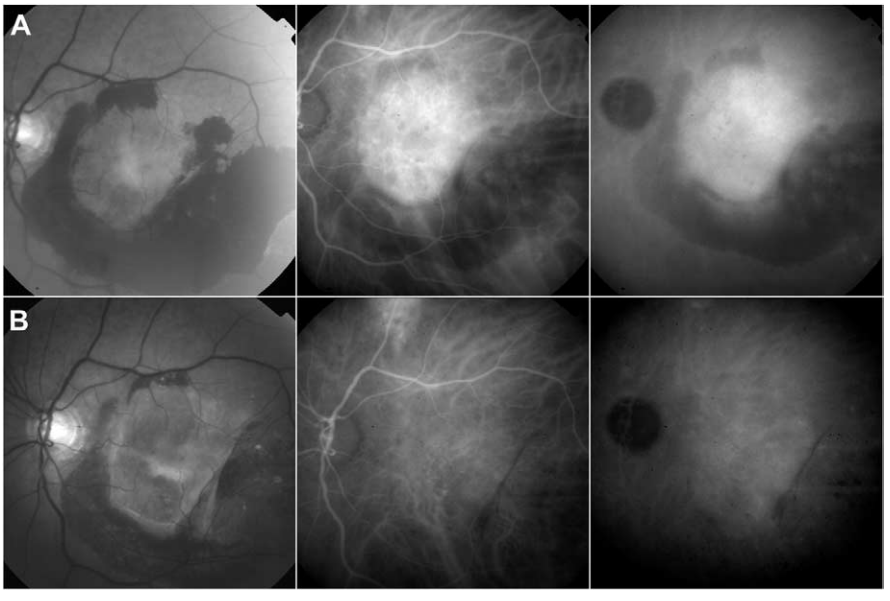

Figure 7. Patient 1, study eye: red-free images with early- and late-phase indocyanine green angiographic images at (**A**) baseline and (**B**) week 12.

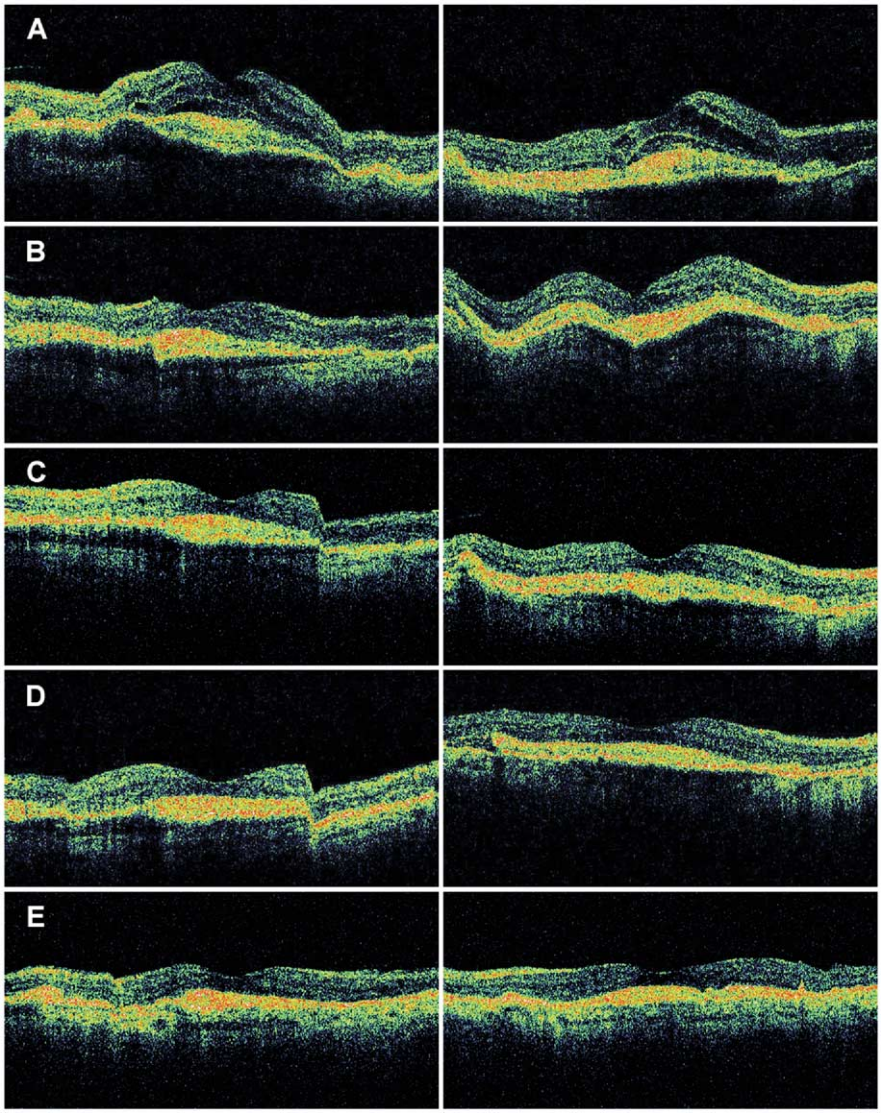

Figure 8. Patient 1, study eye: vertical (left) and horizontal (right) optical coherence tomography scans and central retinal thickness measurements at (**A**) baseline (449 μm), (**B**) week 1 (241 μm), (**C**) week 2 (212 μm), (**D**) week 4 (224 μm), and (**E**) week 12 (193 μm).

angiography showed no evidence of early focal hyperfluorescence in the study eye (Fig 10B).

Discussion

After 3 months, the results from the SANA Study are promising but also very preliminary. In this first cohort of 9 patients receiving 2 or 3 infusions of bevacizumab at a dose of 5mg/kg, systemic bevacizumab was associated with a significant increase in VA and a significant decrease in central retinal thickness as early as 1 week after initiation of therapy. This overall improvement continued through week 12 of the study. Because 8 of the 9 patients had evidence of CNV in both eyes, we expected to observe some benefit to the fellow eyes if a benefit was observed in the study eyes. An overall improvement in VA was observed in the fellow eyes, and there was a good correlation between the increase in VA letter scores and the decrease in central retinal thickness measurements. Although it is impossible to come to a conclusion on any long-term benefits from bevacizumab therapy in a chronic progressive disease like neovascular AMD, it is notable that this treatment for neovascular AMD has been associated with all of the following: (1) a rapid and significant improvement in VA, (2) a significant reduction in central retinal thickness, (3) an absence or marked reduction of fluorescein angiographic leakage from CNV, and (4) a statistically significant correlation between the increase in VA and the decrease in central retinal thickness. Although there was no control group in this study and patients, their doctors, and the vision examiners were not masked to treatment assignment, the convergence of the observed positive outcomes along with the rapid

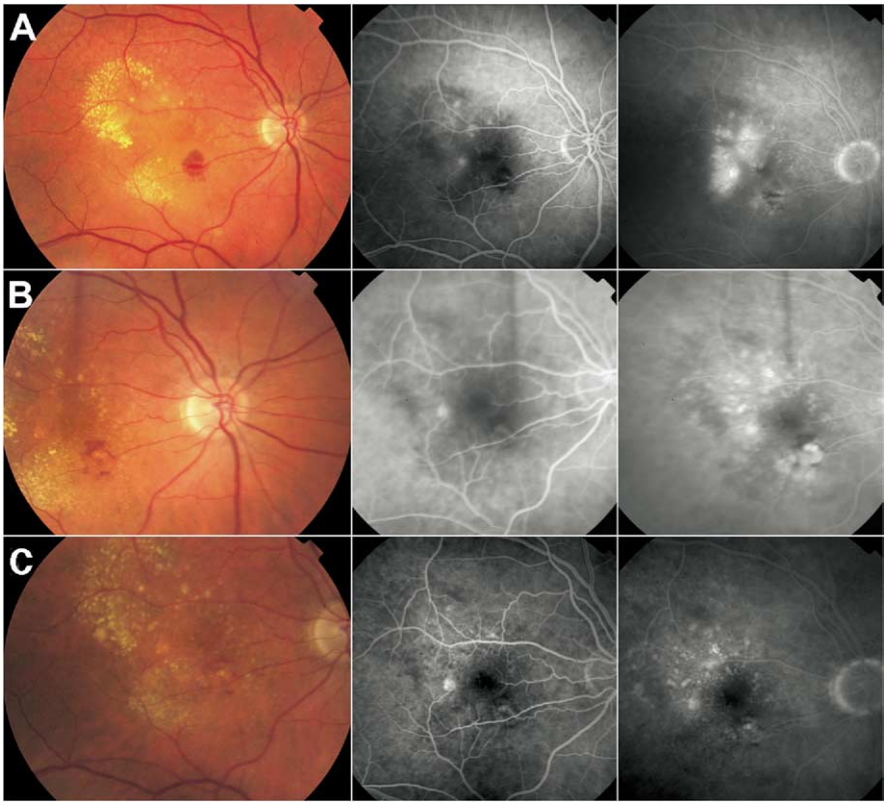

Figure 9. Patient 2, study eye: color fundus photographs with early- and late-phase fluorescein angiographic images at (**A**) baseline and (**B**) week 4 and (**C**) week 12 follow-up visits. Baseline images were taken using a 50° camera setting, whereas follow-up images were taken using the protocol 35° camera setting.

temporal onset of these changes within 1 week of treatment strongly suggest a direct effect of systemic bevacizumab therapy on CNV that is not likely to be explained by the natural history of the disease or by chance alone. Moreover, we are unaware of any previous reports using a systemic anti-VEGF drug in humans for neovascular AMD, and could find no reference to it in a computerized search using PubMed.

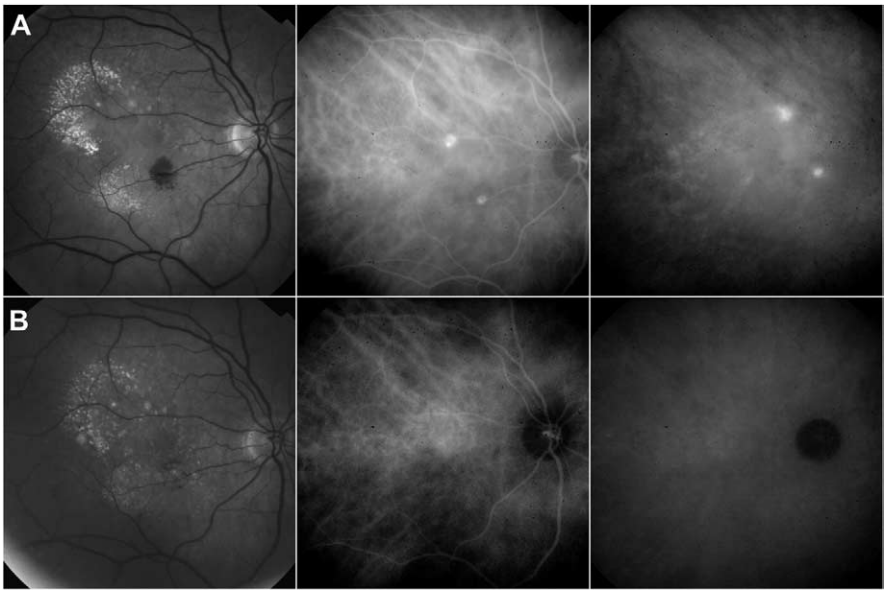

Figure 10. Patient 2, study eye: red-free images with early- and late-phase indocyanine green angiographic images at (**A**) baseline and (**B**) week 12.

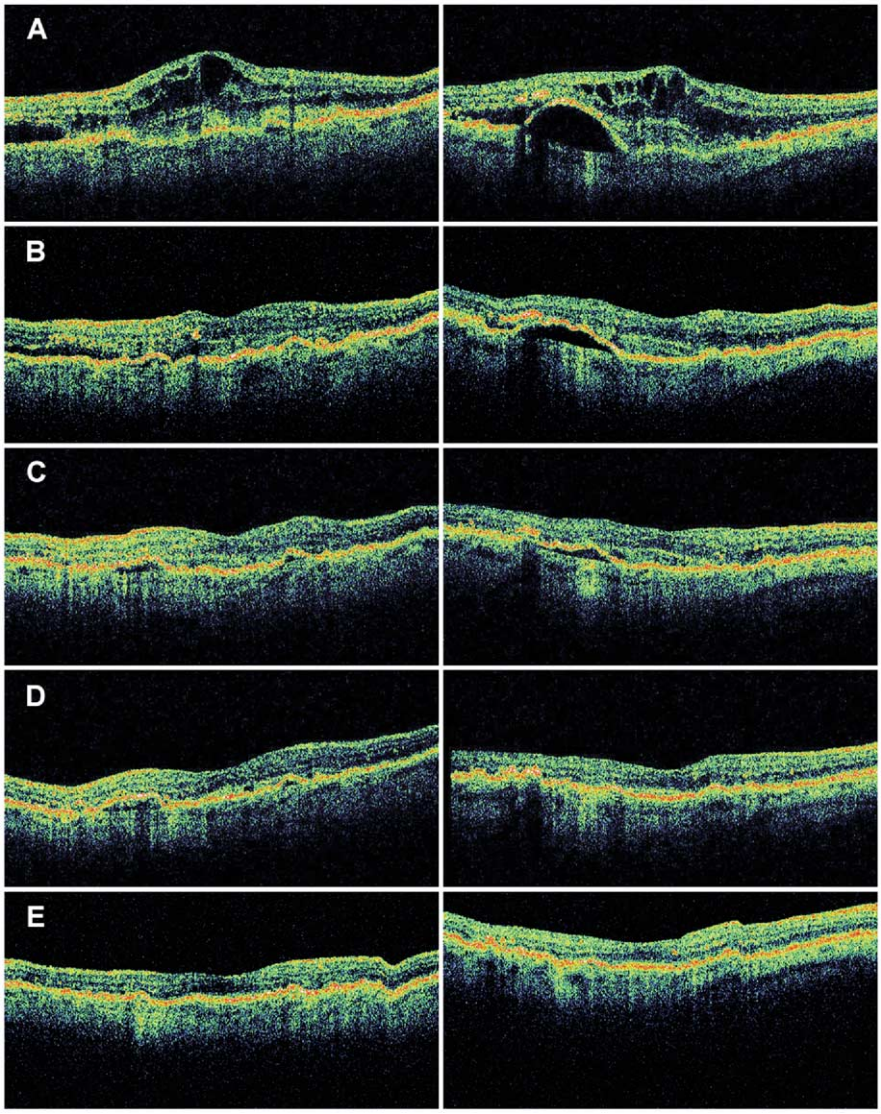

Figure 11. Patient 2, study eye: vertical (left) and horizontal (right) optical coherence tomography scans and central retinal thickness measurements at (**A**) baseline (539 μm), (**B**) week 1 (360 μm), (**C**) week 2 (320 μm), (**D**) week 4 (222 μm), and (**E**) week 12 (212 μm).

Bevacizumab seems to eliminate leakage from CNV and normalize the retinal anatomy in eyes of patients with neovascular AMD after 2 or 3 treatments. A statistically significant correlation was found between the improvement in retinal anatomy and the improvement in VA. Figure 5 depicts this correlation and the variability observed in the extent of vision improvement associated with any given change in central retinal thickness. For example, a decrease in 250 μm was associated with a gain of 5 letters in the study eye of patient 1 and a gain of 34 letters in the fellow eye of patient 5. This variability in the extent of vision improvement may result from the types of neovascular lesions enrolled in the study and the history of treatments performed on these eyes. The eyes enrolled in this study contained lesions that were ineligible for PDT or were not treated with PDT at the patient's discretion. Most commonly, patients who received prior PDT elected not to receive additional PDT because of the vision loss they associated with the previous treatment. Because these lesions were a heterogeneous mix of lesion types with differing sizes, chronicity, and treatment history, it should not be surprising that we observe differences between these eyes in the extent of visual recovery after restoration of retinal anatomy. Important factors that may play a role in the recovery of vision include the lesion type (predominantly classic CNV, minimally classic CNV, occult CNV, and RAP), lesion size, prior PDT and number of prior PDT treatments, prior laser photocoagulation, the presence of intraretinal or subretinal blood, a retinal pigment epithelial detachment or tear, the location of fluid contributing to an increase in central retinal thickness (intraretinal fluid vs. subretinal fluid), and the presence of a cataract. As more patients are enrolled in this study and longer follow-up is obtained, we will begin to identify the most important variables that will help predict the extent of VA improvement.

Although we cannot predict the extent of VA improvement after bevacizumab therapy in only 9 patients with 12 weeks' follow-up, it is noteworthy that significant improvement in retinal anatomy was observed for all the lesions in the study eyes and most of the lesions in the fellow eyes, except those eyes with disciform scars. This improvement in retinal anatomy suggests that VEGF is primarily responsible for the fluid accumulation, and this fluid accumulation is most likely due to increased vascular permeability. It is unclear at this time whether the entire benefit derived from bevacizumab results solely from inhibition of VEGF-induced vascular permeability or whether additional benefit may result from inhibiting formation of CNV or promoting regression of CNV. What seems apparent from these results is that bevacizumab can exit the systemic circulation in the area of the CNV, bind VEGF, and inhibit leakage from CNV. These results also suggest that only 2 or 3 infusions with bevacizumab over 4 weeks can result in a treatment benefit lasting ≥8 additional weeks.

Historically, the focus in treating neovascular AMD has been on the destruction of CNV. However, the positive results from the recent phase II/III trials with pegaptanib sodium and the promising results from other early-phase anti-VEGF therapies suggest that the inhibition of growth and leakage of subfoveal CNV may become the primary focus of therapy, or at least a complementary strategy to be used in conjunction with destructive methods. Our early results with bevacizumab therapy are consistent with the early results obtained using other intravitreal anti-VEGF therapies, but much more needs to be done before concluding that bevacizumab therapy can inhibit leakage and inhibit lesion growth while improving VA outcomes. More importantly, we need to determine the true risks of this therapy in an elderly population to assess whether the potential benefits outweigh these risks.

We propose that a larger study using bevacizumab therapy should be initiated in patients with neovascular AMD. One strategy might be to perform a larger open-label study to determine the risks associated with bevacizumab therapy in neovascular AMD patients. One option may be to offer this therapy to patients who refuse an intravitreal injection and are not eligible for PDT. Alternatively, a trial could be performed on neovascular AMD patients who have lost vision while receiving PDT or pegabtanib therapy due to lesion growth and leakage to determine if salvage therapy with bevacizumab could improve VA, angiographic, and OCT outcomes. Although an obvious selection bias would be introduced in this type of salvage study, it does provide an option for patients who may not have any alternatives. Eventually, a large randomized clinical trial comparing bevacizumab therapy with pegaptanib therapy and/or PDT will be required before adopting systemic bevacizumab as a first-line treatment for neovascular AMD. If systemic bevacizumab therapy proves useful for the treatment of neovascular AMD, patients will have a choice between an intravitreal injection and a systemic infusion of an anti-VEGF drug.

A major advantage of systemic therapy is the ability to deliver the drug at a therapeutic level directly to the target neovascular tissue in the choroid or retina, compared with local therapy, in which the drug needs to penetrate a barrier before reaching the neovascular tissue. Such barriers include the sclera and choroid after a sub–Tenon's capsule injection or the retina and RPE after an intravitreal injection. As a result, drug concentration at the site of neovascularization after local delivery may be difficult to predict and may vary depending upon lesion characteristics such as where the neovascularization is located, the amount of fluid, and the presence of hemorrhage or a RPE detachment. Even with systemic therapy, these lesion characteristics may affect the availability of the drug in the target tissue, but there may be a greater likelihood that a more predictable drug concentration will be present at the actual site of neovascularization. Other advantages of systemic therapy include the elimination of infectious endophthalmitis, retinal detachment, and lens injury as potential risks after an intravitreal injection. An additional advantage of systemic therapy is the ability to treat both eyes simultaneously in patients with bilateral neovascular disease. Another possible advantage may be a more predictable outcome in patients who have undergone a vitrectomy or who are aphakic, in which case the half-life of an intravitreally administered drug is probably diminished,[41] resulting in less drug being available to penetrate the retina and bind VEGF. Although the half-life of bevacizumab in the intravitreal cavity after IV infusion may be diminished as well, at least a systemic drug will perfuse the neovascularization and then diffuse through the extracellular space and bind VEGF before passing into the intravitreal cavity and exiting the eye. In addition, a theoretical advantage of systemic therapy may be the increased durability of the treatment effect and the need for fewer retreatments. In contrast to the drugs that are injected into the eye with a half-life of <7 days (Genentech, Inc., Eyetech Pharmaceuticals, unpublished data), the systemic half-life of bevacizumab is about 20 days.

However, there are major disadvantages associated with systemic bevacizumab therapy. The most significant disadvantage of systemic bevacizumab therapy is the possibility of life-threatening adverse events. According to an FDA warning letter in August 2004,[42] patients with advanced metastatic colorectal cancer receiving concomitant chemotherapy and bevacizumab were at an increased risk of potentially fatal thromboembolic events compared with cancer patients receiving chemotherapy alone. This information was then updated in January 2005.[43] This risk was not initially obvious from the phase III clinical trials that resulted in bevacizumab's approval by the FDA.[35,44] The risk became apparent only after Genentech, Inc. performed a meta-analysis on all clinical trial results using bevacizumab. Overall, the risk of thromboembolic events was approximately 2-fold higher in patients receiving infusions of 5-fluorouracil–based chemotherapy plus bevacizumab, with an estimated overall rate of up to 4.4%. Although the risk of thromboembolic events in elderly cancer patients has been documented, the risk of thromboembolic events in elderly AMD patients receiving intermittent bevacizumab therapy, compared with continual therapy every 2 weeks in cancer patients, is not known. Even if the risk in AMD patients is initially low, as additional treatments are given to our elderly population, the risk of thromboembolic events most likely will increase. As a precaution in our SANA Study,

even before the FDA warning was announced we had excluded patients with a history of cerebrovascular accident, transient ischemic attack, myocardial infarction, angina, or any other thromboembolic disease (Table 1). Moreover, when the FDA warning was announced, all patients were informed of this risk, none of the patients withdrew from the study, and none of our potential subjects decided not to participate. Other potential systemic side effects include hypertension, epistaxis, hemoptysis, and proteinuria, which have been reported in a variety of cancer studies using bevacizumab.[32–35] Of these remaining risks, hypertension was observed in 7 of our 9 patients, but the elevated BP was easily controlled with medication within the first 6 weeks. The reason why no additional increases in BP were observed after week 6 is most likely the final bevacizumab treatment being given at week 4; however, hypertension may become a more chronic problem if bevacizumab is reinfused intermittently or over an extended period of time.

Another risk associated with systemic bevacizumab would be delayed wound healing after surgery. Although none of our patients underwent a major surgical procedure during the first 3 months of this study, it is important that patients be aware of this risk before receiving bevacizumab therapy so that nonelective surgery can be performed before initiation of treatment and elective surgery can be delayed. One patient, patient 3, did undergo uneventful clear cornea cataract surgery and intraocular lens implantation in her fellow eye. Because healing of the avascular cornea is not thought to require VEGF, it is not surprising that her wound closed normally. In this one patient, VA improved significantly after the surgery, and no significant leakage from CNV was detected. Many more patients need to be studied, but this initial result is encouraging and suggests that cataract surgery is safe for patients with neovascular AMD receiving bevacizumab therapy.

One theoretical risk associated with systemic bevacizumab therapy is that VEGF inhibition could be deleterious to the normal eye. Maintenance of the choriocapillaris in a normal eye is believed to require VEGF produced by the RPE.[45] Systemic bevacizumab could, in theory, inhibit this VEGF and cause regression of the choriocapillaris and subsequent vision loss. However, we have observed no evidence of vision loss after 3 months in our study population, and the one patient with dry AMD at baseline (patient 8, fellow eye) maintained 20/20 vision. In addition, using indocyanine green angiography we observed no change in the overall size of plaques and no increase in areas of hypofluorsecence that might be observed if bevacizumab were adversely affecting the choroidal circulation. Although this risk cannot be ignored and may be of concern with chronic administration of bevacizumab to our patients, it is reassuring that there have been no reports of decreased vision among the cancer patients receiving infusions of bevacizumab every 2 weeks for many months.

Due to the potential of fatal thromboembolic events associated with bevacizumab therapy and the small number of patients treated to date with only limited follow-up, we do not recommend the use of bevacizumab outside of a clinical trial until more data regarding efficacy and safety are obtained. However, based on these early results, we feel the potential benefits of systemic bevacizumab may outweigh the risks in patients with neovascular AMD, particularly monocular patients unresponsive to other therapies and patients with bilateral subfoveal CNV. To determine the true risks and benefits of systemic bevacizumab in the elderly population, we need to organize a large multicenter prospective clinical trial. Perhaps lower doses of bevacizumab or less frequent dosing would result in even better outcomes, and these types of modifications to the treatment protocol can be explored in a larger study. While this larger trial is being planned, the SANA Study will continue patient recruitment and follow-up to evaluate the long-term safety, effectiveness, and durability of bevacizumab therapy.

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Appendix

Patient 8 (Case Report and Figures 12–14)

A 73-year-old woman with vision loss in her left eye (study eye) was diagnosed with subfoveal minimally classic CNV consistent with the diagnosis of RAP (Figs 12A, 13A, 14A). There was no evidence of CNV in the right eye. At baseline, BCVAs were $20/80^{+1}$ in her study eye and $20/20^{-1}$ in her fellow eye. Central retinal thicknesses on OCT were 412 μm in the study eye (Fig 14A) and 249 μm in the fellow eye. The patient received 3 IV infusions of bevacizumab at 2-week intervals. Visual acuity remained stable in the study eye at week 1 and gradually improved to 20/20 by week 12. The fellow eye vision remained stable at 20/20 through week 12. In the study eye, fluorescein angiography demonstrated an absence of leakage from the CNV by week 12 (Fig 12). Indocyanine green angiography showed early focal hyperfluorescence (hot spot) in the study eye at baseline that was absent from the angiogram performed at week 12 (Fig 13). The central retinal thickness decreased by 95 μm at week 1 and by 143 μm at week 12 (Fig 14), with resolution of the pigment epithelial detachment and cystic maculopathy observed at baseline. In the fellow eye, the central retinal thickness showed no change through week 12.

Patient 9 (Case Report and Figures 15–20)

An 80-year-old woman with vision loss was diagnosed with subfoveal minimally classic CNV in both eyes. Because the lesions were initially smaller than 4 Macular Photocoagulation Study disc areas, she received prior PDT to both eyes, with the right eye receiving 2 treatments and the left eye 1. The second treatment to the right eye was combined with an intravitreal injection of triamcinolone acetonide, and she subsequently developed steroid-induced ocular hypertension in the right eye, which was controlled with topical medication. After PDT, vision loss continued in both eyes secondary to leakage from CNV. At baseline for this study, her right eye (study eye) was diagnosed as a minimally classic CNV lesion with characteristics of a retinal angiomatous proliferation (Figs 15A, Figs 16A, Figs 17A). Her left eye (fellow eye) was diagnosed as a minimally classic CNV lesion (Fig 18A). At baseline, BCVAs were $20/160^{+1}$ in her study eye and $20/80^{-2}$ in her fellow eye. Central retinal thicknesses on OCT were 569 μm in the study eye and 255 μm in the fellow eye (Figs 17A, 20A). The patient received 2 IV infusions of bevacizumab at 2-week intervals. No further infusion was given at week 4, due to the absence of leakage from CNV as assessed by fluorescein angiography and OCT (Figs 15B, 17D). Visual acuity improved in the study eye to $20/80^{+1}$ at week 1 and improved further to $20/63^{+1}$ at week 12. The fellow eye vision improved to $20/63^{+1}$ at week 1 and further to 20/40 at week 12. In the study eye, central retinal thickness decreased by 263 μm at week 1 and by 326 μm at week 12 (Fig 17), with resolution of the pigment epithelial detachment observed at baseline and almost complete resolution of the cystic maculopathy, except for a central area of retinal thickening due to vitreomacular traction. In the fellow eye, the central retinal thickness decreased by 34 μm at week 1 and by 103 μm at week 12 (Fig 20). Fluorescein angiography showed an absence of leakage from the study eye at week 4, which continued through week 12 (Fig 15B, C). Indocyanine green angiography showed early hot spots in the study eye that were absent from the angiogram performed at week 12 (Fig 16). Fluorescein angiography showed staining but an absence of leakage from the fellow eye at week 4, which continued through week 12 (Fig 18). The plaque in the fellow eye observed by indocyanine green angiography appeared less hyperfluorescent, with better delineation and no growth by week 12 (Fig 19).

Table 2. Lesion Characteristics: Study Eyes and Fellow Eyes

	Study Eye		Fellow Eye	
Patient	*Fluorescein Angiographic Classification**	*Prior PDTs*	*Fluorescein Angiographic Classification**	*Prior PDTs*
1	LE: large predominantly hemorrhagic lesion post-PDT (>20 MPS DAs)	1	RE: disciform scar with leakage	1
2	RE: minimally classic CNV (RAP lesion) (5.5 MPS DAs)	0	LE: small recurrence along inferior edge of laser scar (<1 MPS DA)	0
3	RE: minimally classic CNV (13 MPS DAs)	0	LE: disciform scar	0
4	RE: minimally classic CNV with large pigment epithelial detachment (10.5 MPS DAs)	0	LE: disciform scar with leakage	0
5	RE: classic-appearing CNV post-PDT (6.0 MPS DAs)	1	LE: disciform scar with leakage	0
6	LE: predominantly hemorrhagic, classic-containing lesion post-PDT (10.8 MPS DAs)	3	RE: disciform scar with leakage post–laser coagulation	0
7	RE: classic-appearing CNV post-PDT (1.0 MPS DAs)	2	LE: classic-appearing recurrent CNV post–laser coagulation and post-PDT (5.1 MPS DAs)	1
8	LE: minimally classic CNV (RAP lesion) (4.6 MPS DAs)	0	RE: no CNV	0
9	RE: minimally classic-appearing CNV post-PDT (4.5 MPS DAs)	2	LE: minimally classic-appearing CNV post-PDT (9.5 MPS DAs)	1

CNV = choroidal neovascularization; LE = left eye; MPS DAs = Macular Photocoagulation Study disc areas; PDT = photodynamic therapy; RAP = retinal angiomatous proliferation; RE = right eye.
*Classification of CNV after PDT may be ambiguous.

Table 5. Fellow Eyes: Change in Visual Acuity through 12 Weeks

Patients' Fellow Eyes (N = 8)	**Baseline Visual Acuity Letters (Snellen Equivalent)**	**Week 1 Visual Acuity Letters (Snellen Equivalent)**	**Week 6 Visual Acuity Letters (Snellen Equivalent)**	**Week 12 Visual Acuity Letters (Snellen Equivalent)**	**Change in Visual Acuity Letter Scores from Baseline to Week 12**
Median (*P* value)*	30 (20/250)	33 ($20/250^{+3}$) (0.67)	54 ($20/80^{-1}$) (0.012)	57 ($20/80^{+2}$) (0.018)	27 (5.4 lines)
Mean (*P* value)†	40 (20/160)	41 ($20/160^{+1}$) (0.41)	54 ($20/80^{-1}$) (0.006)	56 ($20/80^{+1}$) (0.012)	16 (3.2 lines)

Patient 3 was not included in median and mean calculations. Patient 3 underwent cataract surgery after week 6 in the study, resulting in a vision improvement of 37 letters.
*Paired Wilcoxon signed rank test.
†Paired Student's *t* test.

Table 6. Fellow Eyes: Change in Central Retinal Thickness through 12 Weeks

Patients' Fellow Eyes (N = 6)	Baseline Central Retinal Thickness (μm)	Week 1 Central Retinal Thickness (μm)	Week 6 Central Retinal Thickness (μm)	Week 12 Central Retinal Thickness (μm)	Decrease in Central Retinal Thickness (μm) from Baseline to Week 12
Median (*P* value)[†]	252	238 (0.028)	194 (0.046)	193 (0.028)	59
Mean (*P* value)[‡]	282	231 (0.12)	196 (0.097)	190 (0.06)	92

In 3 patients (3, 4, and 6), retinal boundaries could not be identified at baseline due to advanced cataract (patient 3) and disciform scarring (patients 4 and 5) resulting in unreliable central retinal thickness measurements using the Stratus OCT algorithm.
[†]Paired Wilcoxon signed rank test.
[‡]Paired Student's *t* test.

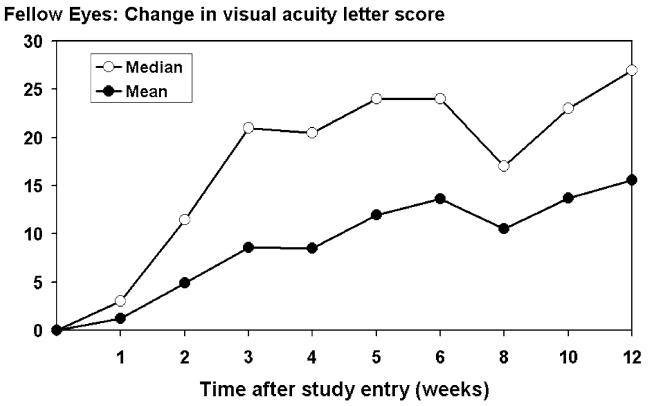

Figure 3. Fellow eyes: median and mean change in visual acuity letter scores through 12 weeks (5 letters = 1 line).

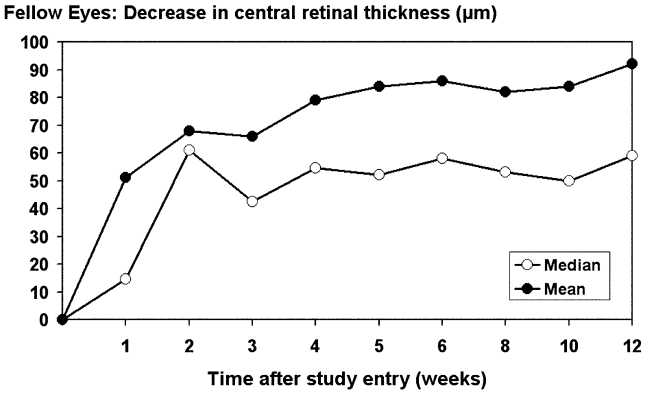

Figure 4. Fellow eyes: median and mean change in the central 1-mm retinal thickness of the macula, as measured by optical coherence tomography, through 12 weeks.

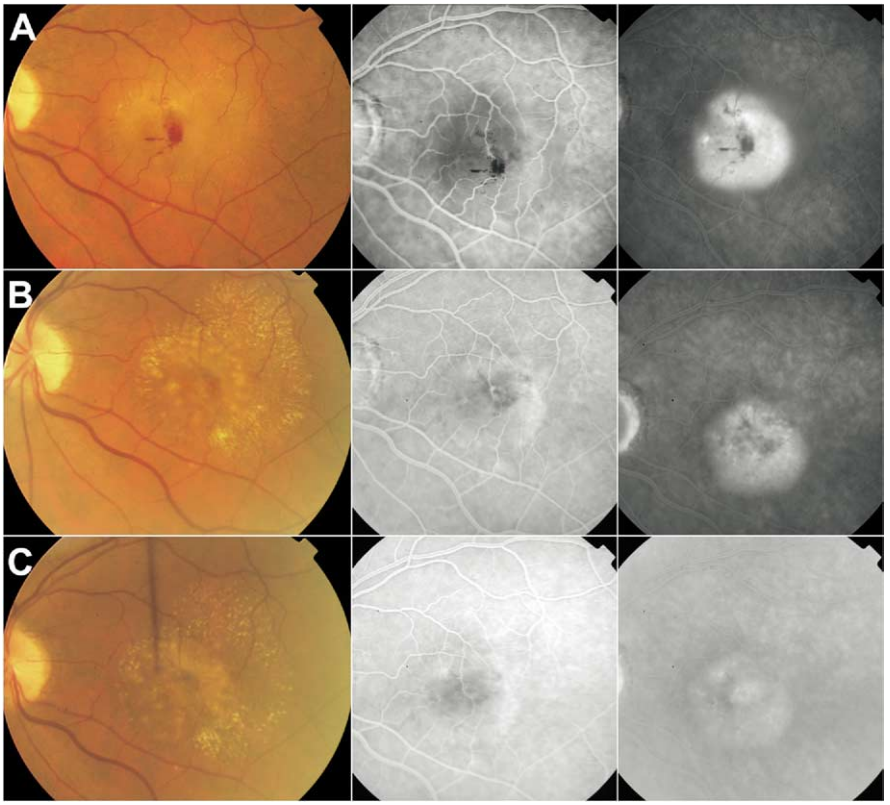

Figure 12. Patient 8, study eye: color fundus photographs with early- and late-phase fluorescein angiographic images at (**A**) baseline, (**B**) week 4, and (**C**) week 12.

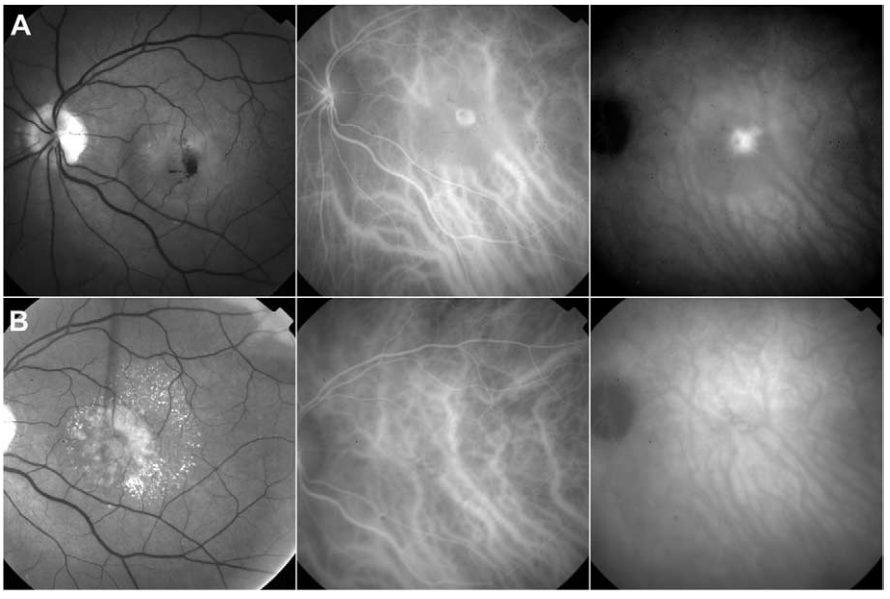

Figure 13. Patient 8 study eye: red-free images with early- and late-phase indocyanine green angiographic images at (**A**) baseline and (**B**) week 12.

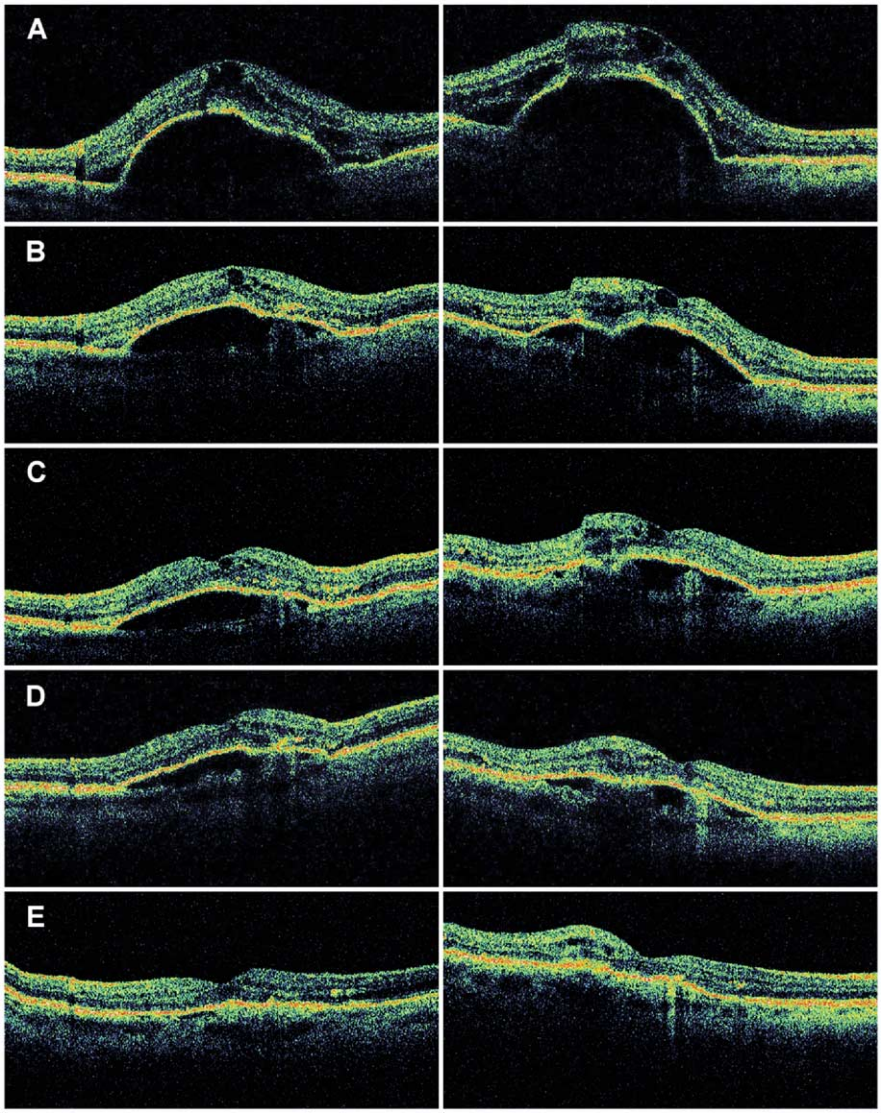

Figure 14. Patient 8, study eye: vertical (left) and horizontal (right) optical coherence tomography scans and central retinal thickness measurements at (**A**) baseline (412 μm), (**B**) week 1 (317 μm), (**C**) week 2 (270 μm), (**D**) week 4 (268 μm), and (**E**) week 12 (269 μm).

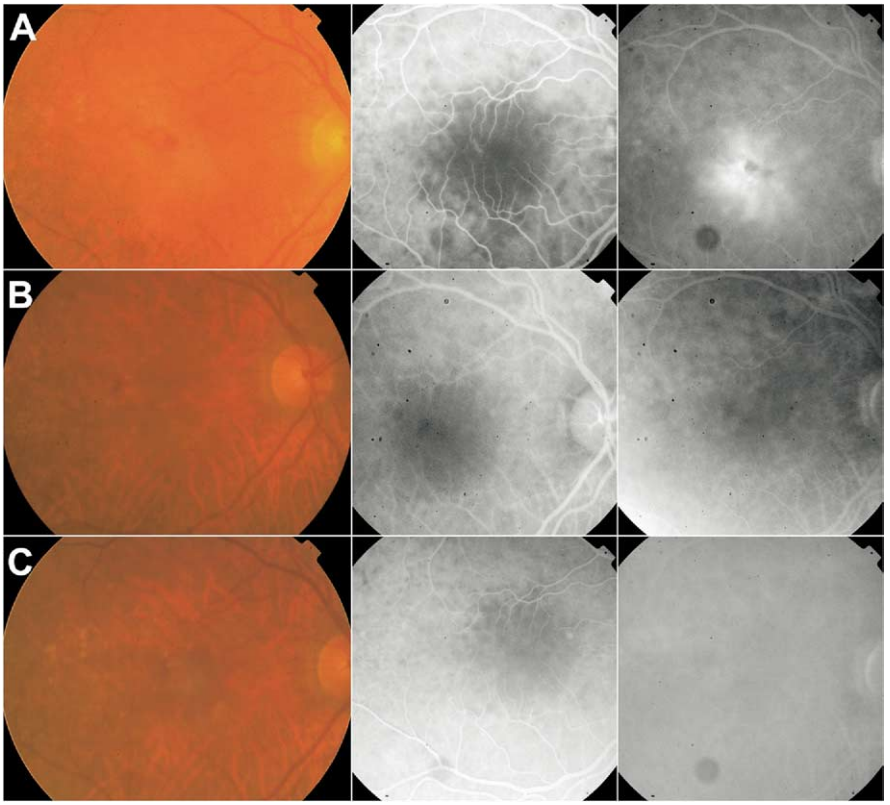

Figure 15. Patient 9, study eye: color fundus photographs with early- and late-phase fluorescein angiographic images at (**A**) baseline, (**B**) week 4, and (**C**) week 12.

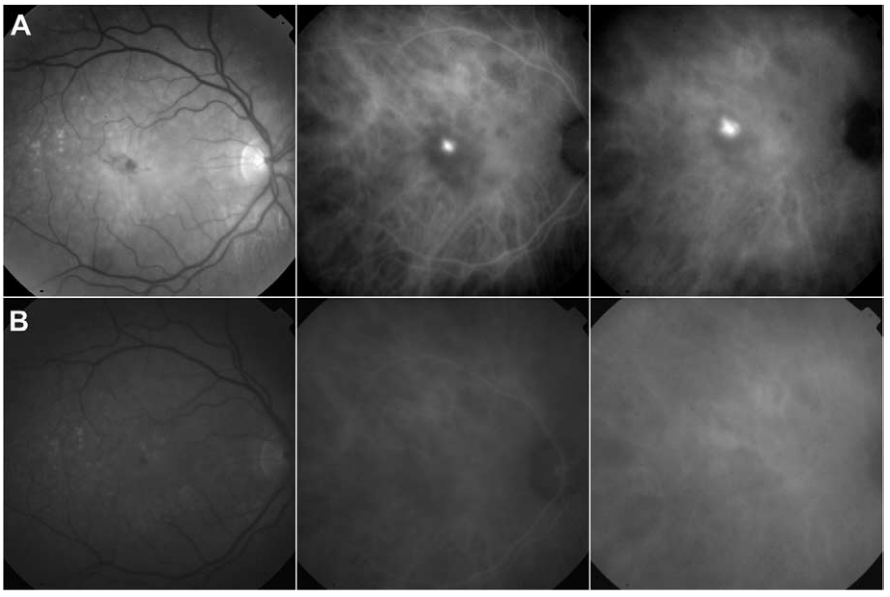

Figure 16. Patient 9, study eye: red-free image with early- and late-phase indocyanine green angiographic images at (**A**) baseline and (**B**) week 12.

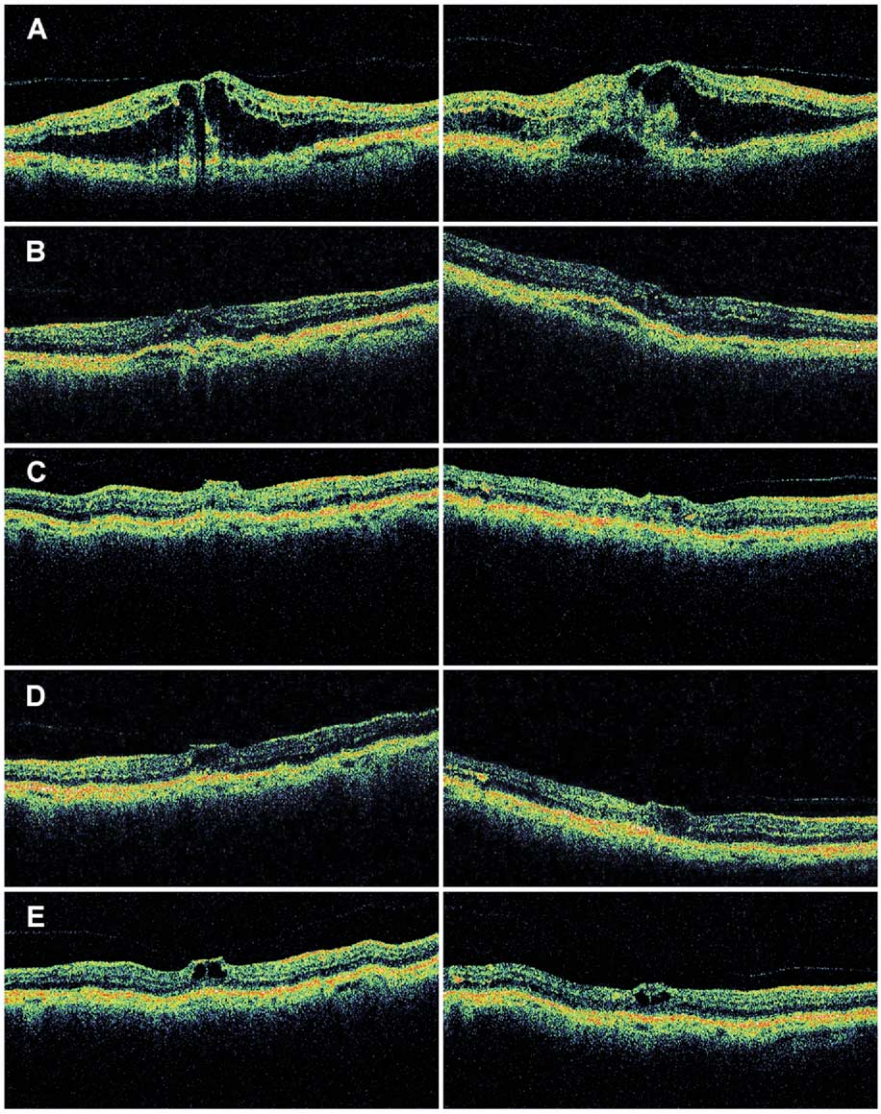

Figure 17. Patient 9, study eye: vertical (left) and horizontal (right) optical coherence tomography scans and central retinal thickness measurements at (**A**) baseline (569 μm), (**B**) week 1 (306 μm), (**C**) week 2 (256 μm), (**D**) week 4 (253 μm), and (**E**) week 12 (243 μm).

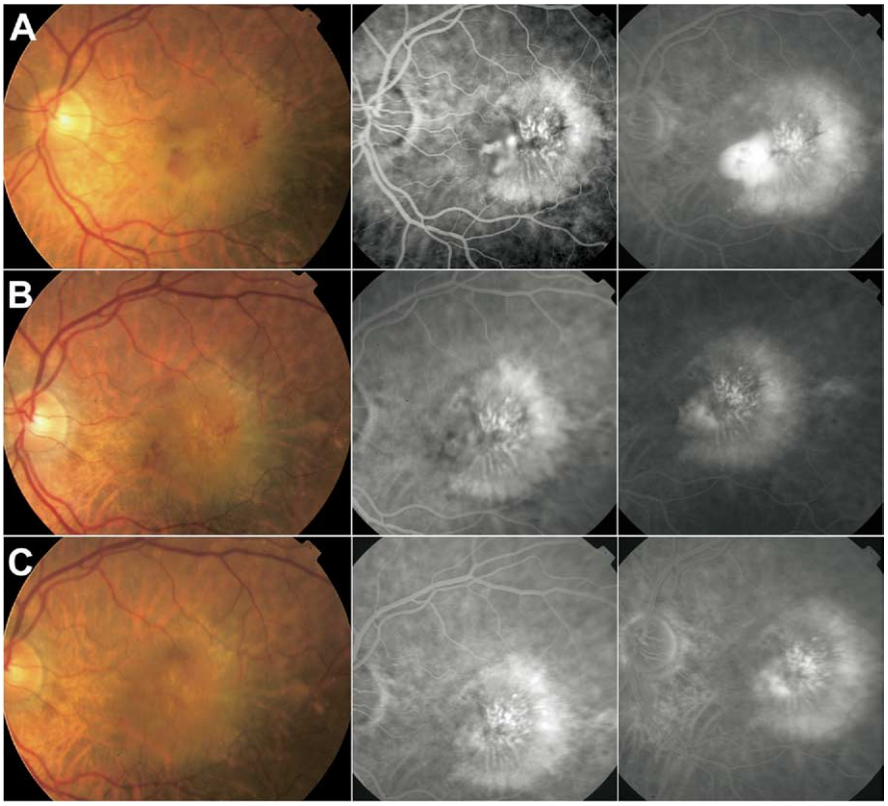

Figure 18. Patient 9, fellow eye: color fundus photographs with midphase and late-phase fluorescein angiographic images at (**A**) baseline, (**B**) week 4, and (**C**) week 12.

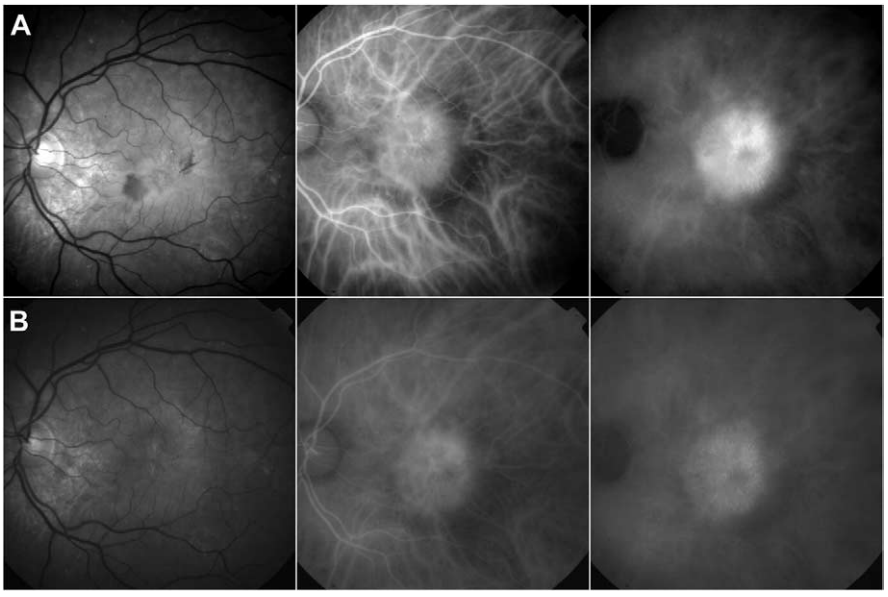

Figure 19. Patient 9, fellow eye: red-free image with early- and late-phase indocyanine green angiographic images at (**A**) baseline and (**B**) week 12.

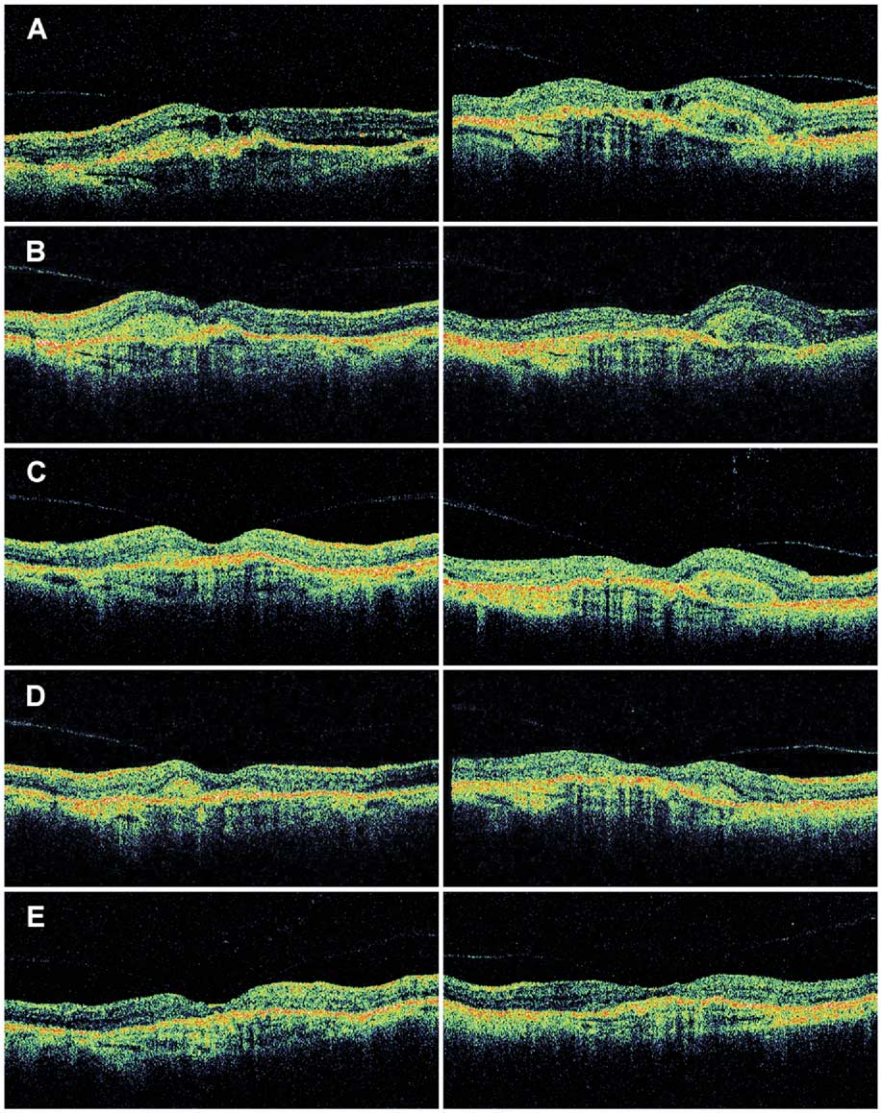

Figure 20. Patient 9, fellow eye: vertical (left) and horizontal (right) optical coherence tomography scans and central retinal thickness measurements at (**A**) baseline (255 μm), (**B**) week 1 (221 μm), (**C**) week 2 (163 μm), (**D**) week 4 (155 μm), and (**E**) week 12 (152 μm).