

Prospective Study of Intravitreal Ranibizumab as a Treatment for Decreased Visual Acuity Secondary to Central Retinal Vein Occlusion

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- **PURPOSE:** To evaluate intravitreal injection of ranibizumab as a potential treatment for decreased visual acuity (VA) secondary to central retinal vein occlusion (CRVO).
- **DESIGN:** Prospective, interventional case series.
- **METHODS:** Patients with CRVO prospectively recruited from a practice were administered intravitreal ranibizumab 0.5 mg (Lucentis; Genentech Inc, South San Francisco, California, USA) at baseline and monthly for two additional doses. The patients were given additional ranibizumab if they had macular edema as determined by optical coherence tomography or any new intraretinal hemorrhage. Patients were evaluated for number of required injections, side effects, changes in VA, and macular thickness.
- **RESULTS:** There were 20 eyes of 20 patients who at baseline had a mean age of 72.1 years, a mean VA of 45.8 Early Treatment of Diabetic Retinopathy letters, and a mean central macular thickness of 574.6 μm . Of the 20 eyes, five previously had received intravitreal triamcinolone and 11 had received intravitreal bevacizumab (Avastin; Genentech Inc). At 12 months of follow-up, the mean VA improved to 64.3 letters and the central macular thickness decreased to 186 μm (both different than baseline values; $P < .001$) using a mean of 8.5 injections. The change in macular thickness was not correlated with the change in VA. In one patient with a history of transient ischemic attack, an ischemic stroke developed but no sequela resulted. In another patient, vitreomacular traction developed, but the patient had improved acuity as compared with baseline. There were no infections, retinal tears, or detachments.
- **CONCLUSIONS:** Intravitreal ranibizumab used over a period of one year improved mean VA, with low rates of adverse events, in patients with CRVO. (Am J Ophthalmol 2009; 147:298–306. © 2009 by Elsevier Inc. All rights reserved.)

CENTRAL RETINAL VEIN OCCLUSION (CRVO) IS A condition characterized by dilation and tortuosity of the retinal venules with hemorrhages in all four quadrants of the retina. Often there is concomitant optic

nerve swelling and macular edema, and there may be exudative detachment of the retina, neovascularization of the iris, and neovascular glaucoma. After diabetic retinopathy, CRVO is the second most common retinal vascular disease affecting the retina.^{1,2} Patients with CRVO report difficulty with many aspects of daily life and have decreased vision-related quality of life as measured by the 25-item National Eye Institute Visual Function Questionnaire.³

Intravitreal levels of vascular endothelial growth factor (VEGF) in CRVO are the highest of those measured in retinal vascular disease,⁴ and the severity of findings in CRVO is proportional to intravitreal VEGF levels.⁵ Retinal neovascularization is seen rarely in eyes with CRVO. Almost all of the features of CRVO can be induced in primate eyes by intravitreal injection of VEGF, including vascular dilation, tortuosity, intraretinal hemorrhage, and capillary nonperfusion.⁶ Intravitreal VEGF injections in primates cause little or no retinal neovascularization.⁶ Inhibiting VEGF would seem to be a rational strategy for treating CRVO. Intravitreal injection of anti-VEGF agents caused regression of iris neovascularization.^{7,8} CRVO was among the first diseases treated with intravitreal bevacizumab (Avastin; Genentech Inc, South San Francisco, California, USA),⁹ and subsequent case series showed a large proportion of patients having visual acuity (VA) improvement.^{10,11} Bevacizumab treatment early after the onset of CRVO was associated with a statistically significant reduction in venous dilation, tortuosity, optic disc swelling, and macular edema in addition to improvement of VA.¹² Ranibizumab (Lucentis; Genentech Inc) has potentially increased retinal penetration because of a smaller molecular size and a higher binding affinity for VEGF than does bevacizumab.¹³ Given these potential attributes, ranibizumab may be particularly suited as an agent to treat CRVO, a disease with manifestations that seem to be driven by VEGF. To gain preliminary information, we performed a prospective study of intravitreal ranibizumab injections as a treatment for decreased VA secondary to CRVO.

METHODS

THIS WAS A PROSPECTIVE, PHASE 1, OPEN-LABEL STUDY examining intravitreal injection of ranibizumab 0.5 mg as a treatment for decreased VA resulting from CRVO. The

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study had Food and Drug Administration (FDA) Investigator Investigational New Drug number 100,240.

The patients with CRVO (as manifested by retinal hemorrhages and dilated retinal venules in all four quadrants of the fundus) underwent a comprehensive ophthalmologic examination that included VA assessment using Early Treatment of Diabetic Retinopathy (ETDRS) protocol refraction measured at 4 m, slit-lamp biomicroscopy, indirect ophthalmoscopy, color fundus photography, optical coherence tomography (OCT) using the Stratus OCT (Carl Zeiss Meditec, Dublin, California, USA), and fluorescein angiography (FA). The central macular thickness (CMT) was measured manually using the software calipers because of the known inaccuracies of the segmentation algorithm with the Stratus OCT software.¹⁴ Digital FA was performed with a Topcon TRC-50DX fundus camera with ImageNet software (Topcon USA; Paramus, New Jersey, USA). FA was performed by positioning the patient at the fundus camera, injecting 2 ml of a 25% solution of sodium fluorescein (Akorn Inc, Somerset, New Jersey, USA) as a bolus into the antecubital vein. The timer on the camera was started at the time of injection, and filling, mid-phase, and late-phase images were recorded. The angiograms were evaluated for what was termed *arm-to-early arterial filling*, which was the time in seconds from the injection to when the dye front within the superior and inferior temporal arcade arterioles both were seen to extend temporal to the retinal midline as defined by a vertical line extending through the geometric center of the fovea. Late-phase angiograms were evaluated for the presence of leakage and for the accumulation of dye within the retina.

Patients with decreased VA secondary to CRVO were eligible for the study if they were 18 years or older and had a VA score of 34 letters (20/200) or more and 73 letters (20/40) or less as determined by the ETDRS VA protocol. To be eligible for the study, the patients must have had macular edema with a thickness of more than 250 μm . Patients who were pregnant, had uncontrolled hypertension or diabetes, had greater than moderate nonproliferative diabetic retinopathy, uncontrolled glaucoma, OCT evidence of a vitreoretinal interface abnormality, or any other additional ocular diseases that could compromise irreversibly the VA of the study eye were excluded from the study. Additionally, patients were not eligible for the study if they had a history of vitreous surgery or intravitreal, peribulbar, or retrobulbar corticosteroids within six months, cataract surgery within six months, yttrium–aluminum–garnet capsulotomy within two months, intravitreal injection of pegaptanib sodium within 45 days, or intravitreal injection of bevacizumab within 30 days of enrollment in the study.

Enrolled patients were injected at baseline with 0.5 mg ranibizumab into the vitreous cavity on a monthly basis for the following two months and then were examined monthly. Patients were injected using aseptic technique as per the package labeling for ranibizumab, with the exception that no draping was used. Patients were examined within a

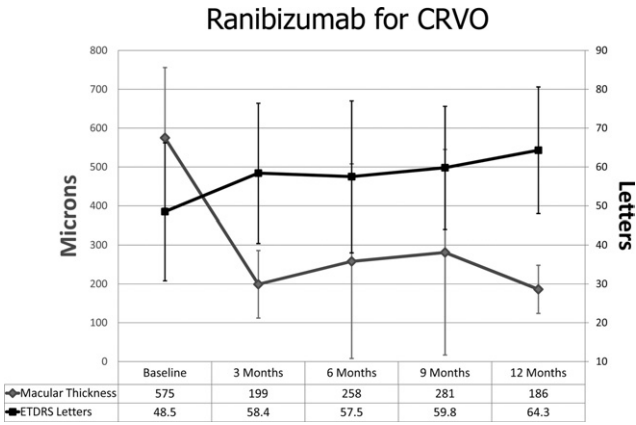


FIGURE 1. Graph showing the thickness of the central macula in micrometers and the visual acuity (VA) in Early Treatment of Diabetic Retinopathy Study letters. CRVO = central retinal vein occlusion.

period from three to seven days after injection at the beginning of the study, but this early examination was eliminated from the protocol after obtaining an exemption from the FDA approximately halfway through the study. Patients were examined on a monthly basis over the course of a one-year follow-up with ETDRS VA, slit-lamp biomicroscopy, indirect ophthalmoscopy, color fundus photography, OCT, and FA. Patients were reinjected with 0.5 mg ranibizumab if they had evidence of any hemorrhage in the retina, or macular edema as determined if there was the presence of a macular thickness of more than 250 μm or intraretinal cystoid spaces within the macular region.

• **STATISTICAL METHODS:** The data obtained were analyzed with frequency and descriptive statistics. Categorical analysis was performed using the Chi-square test. The Pearson correlation coefficient was calculated as a measure of the bivariate linear association between variables. Baseline VA as measured in ETDRS letters was compared with the measurements obtained at three and six months with a paired-samples *t* test. A *P* value of less than .05 was considered significant, except for the VA data, because two evaluations, one at three months and another at six months, were made. (The α was adjusted as per the Bonferroni technique.) There was case-wise deletion of missing data. Statistical analysis was performed with SPSS software version 16.01 (SPSS Inc, Chicago, Illinois, USA).

• **EARLY EXIT FROM STUDY:** Four patients exited the study before the 12-month follow-up. One patient found the travel necessary for the study visits too difficult, another patient moved to a different state for employment reasons and could not return for examinations. In one patient, focal vitreomacular traction developed and the patient underwent vitrectomy, and another patient was presumed to have a stroke, after which she did not want to receive any additional injections. The latter two patients are detailed in the Results. Exited



FIGURE 2. Images obtained from a 53-year-old male with a one-day history of CRVO. (Top left) Fundus photograph showing optic nerve head hyperemia and swelling, dilated tortuous veins, intraretinal hemorrhage, and foveal pseudocyst. (Top right) Fundus photograph obtained at the one-year follow-up showing the manifestations of the CRVO resolved. (Middle left and right) Optical coherence tomography (OCT) images obtained at baseline and at the one-year of follow-up showing dramatic resolution of the macular edema. (Bottom left) Midphase fluorescein angiogram (FA) showing a normal appearance grossly. (Bottom right) However on closer examination, there was a moth-eaten appearance of the capillary bed with very small areas of nonperfusion (arrows). The patient's VA improved 22 letters.

patients were not included in any calculations past the examinations they completed.

RESULTS

• **BASELINE CHARACTERISTICS:** There were 20 eyes of 20 patients who at baseline had a median age of 72.1 years (interquartile range, 60.2 to 80.1 years). Twelve of the patients were male. Of the 20 patients 14 (70%) had hypertension, two (10%) had diabetes mellitus, two (10%) had a history of myocardial infarction, one (5%) had a prior history of a transient ischemic attack, one (5%) was a current smoker, and seven (35%) were former smokers. The median duration of the CRVO on entry to the study was 34.6 weeks (interquartile range, six to 75.5 weeks). Of the 20 patients, 11

had previous treatment, five had previous intravitreal triamcinolone treatment, and 11 (including all of those who had intravitreal triamcinolone treatment) had intravitreal bevacizumab treatment. The median number of past injections for those who received intravitreal bevacizumab was six (interquartile range, 4 to 9; mean, 6.2), with the dose being either 1.25 or 2.5 mg. The median time from the last bevacizumab injection until entry into the study was 58 days (interquartile range, 36.8 to 89 days). The mean baseline VA was 45.8 ETDRS letters (± 17.7 [standard deviation (SD)]; median, 54 letters) and the mean CMT was 574.6 μm (± 181 [SD]; median, 581 μm). The baseline VA and CMT did not differ by previous history of bevacizumab injection ($P = .47$ and $P = .78$, respectively). The FAs showed an arm-to-early arterial filling time occurring at a mean of 28.1 seconds after injection (range, 18.7 to 51.9 seconds). Retinochoroidal

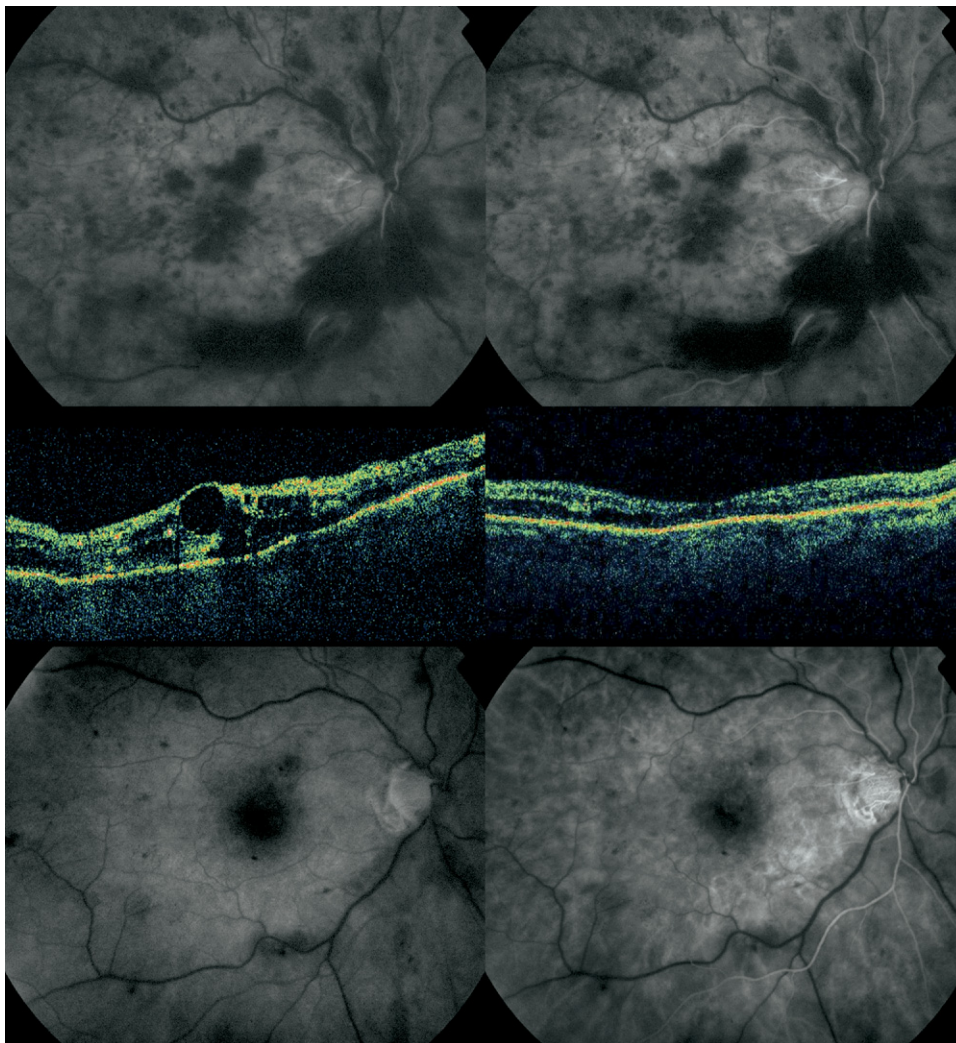


FIGURE 3. Images obtained from a 64-year-old man with a 52-week history of CRVO for which he had not received treatment. (Top left) FA obtained 32.5 seconds after an antecubital injection of fluorescein showing that the dye front is first becoming visible in the eye. (Top right) FA obtained at 33.9 seconds after dye injection showing that the dye front in both the inferior and superior arcade vessels has moved temporal to the midline through the center of the fovea. (Middle left) OCT image showing that the patient had macular edema at baseline. (Middle right) OCT image showing that at the 12-month follow-up, there was no macular edema. (Bottom left) FA obtained at the 12-month follow-up showing the dye front first becoming visible on the vessels on the nerve head at 32.3 seconds. (Bottom right) FA obtained at the 12-month follow-up showing that the dye front moved past the midline at 34.8 seconds after injection. The patient's VA improved 29 letters.

collateral vessels were seen in 11 eyes and were not seen in three eyes, and determination was not possible in six eyes because of hemorrhage on or around the nerve.

• **EARLY FOLLOW-UP:** In the follow-up during the first week after the first injection, the mean VA improved 8.3 letters ($P < .001$) and the CMT decreased by a mean of 349.2 to 225.4 μm of thickness ($P < .001$). The baseline fluorescein arm-to-early arterial filling time was correlated to change in VA at one week ($r = 0.59$; $P = .015$), but did not show a significant correlation with the change in CMT ($r = 0.27$; $P = .3$) at one week. At one month, the vision and thickness parameters regressed to a VA improvement

of 6.2 letters over baseline and a CMT of 273 μm ($P = .019$ and $P < .001$, respectively, as compared with baseline). One patient had a four-letter gain at one week, but an 18-letter loss at one month. He ultimately received nine injections over 12 months and had a 15-letter gain. At the three-month follow-up, the VA showed a mean improvement of 10.4 letters over baseline ($P = .001$), and there was a decrease of the CMT to 199 μm ($P < .001$).

• **TWELVE-MONTH FOLLOW-UP:** At 12 months of follow-up, the mean VA improved to 64.3 letters (median, 68.5 letters), and the CMT decreased to 186 μm (median, 170 μm ; $P < .001$ for each; Figure 1). The patients received a

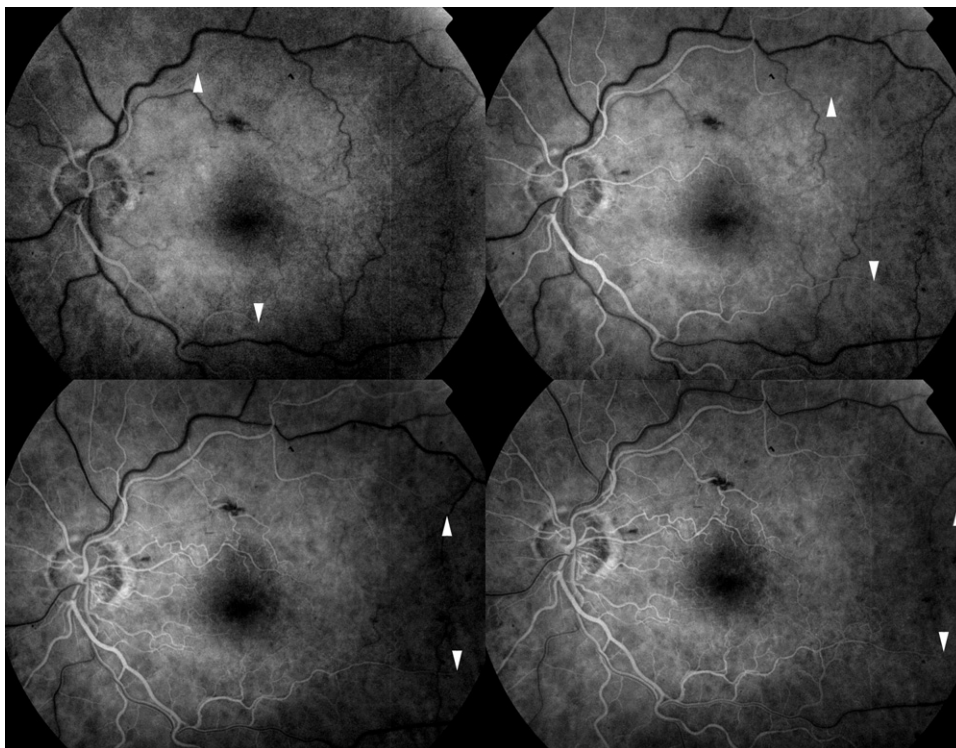


FIGURE 4. (Top left) FA obtained at the 12-month follow-up examination showing that the manifestations of the CRVO have resolved except for a small number of scattered intraretinal hemorrhages (arrows) in this 73-year-old male. At 35 seconds after the antecubital injection of fluorescein, the dye front is visible in the arterioles of the vascular arcade (arrowheads). (Top right) FA showing that the dye front has moved distally within the vessels (arrowheads) by 38.6 seconds. (Bottom left) FA showing that the dye front has moved distally within the vessels (arrowheads) by 43.6 seconds after injection. (Bottom right) FA showing that the dye front has nearly moved out of the frame (arrowheads) by 47.9 seconds after injection. The patient's VA improved six letters.

mean number of 8.5 injections (median, 10). Considering the patients who exited early from the study, the injection frequency was 0.85 per month over the total potential months in which injection was possible, with 47.3% of the injections given for edema and 52.7% given principally because of hemorrhage criteria. The change in VA was not correlated with the number of injections ($r = 0.39$; $P = .14$). Although both the VA and the CMT improved, the two measures were not correlated ($r = 0.24$; $P = .38$). There were nine (56.3%) eyes that had improvement of three lines or more, and two eyes (12.5%) that had an improvement of more than six lines of VA. The mean last observation carried forward acuity was 63 letters. There was one eye (6.3%) with a loss of three lines or more at 12 months (that eye had a 20-letter loss). This eye had recurrence of macular edema after one month without an injection of ranibizumab when the acuity was 21 letters better. As part of an extension study, this patient had an injection of ranibizumab at 12 months and had a return of vision during that study (data not shown).

The change in VA at one week was correlated with the change in acuity at 12 months ($r = 0.56$; $P = .029$), but the change at one month was not correlated with the change in acuity at 12 months ($r = 0.37$; $P = .16$). The change in CMT at one week was correlated with the change in macular

thickness at 12 months ($r = 0.94$; $P < .001$). The change in CMT at one month showed a smaller correlation with the change in CMT at 12 months ($r = 0.5$; $P = .047$). The change in VA at 12 months was not correlated with the arm-to-early arterial filling time at baseline ($r = 0.11$; $P = .69$). There was no difference in the VA change among those who had previous bevacizumab treatment vs those who did not ($P = .61$). In one patient, retinochoroidal collateral vessels developed, and in none of the patients with retinochoroidal collateral vessels at baseline did they disappear by 12 months. The mean arm-to-early arterial filling time at the final examination was 29.2 seconds, a change from baseline that was not significant ($P = .9$). Although not numerically quantified, cotton wool spots were seen to take many months to resolve in this series. At 12 months, examination of the FAs showed capillary network in the retina had a moth-eaten appearance with telangiectasis (Figures 2 through 5).

• **SAFETY:** There were a total of 170 intravitreal injections over the study period, and there were no retinal tears, detachments, or infections resulting from these injections. One 84-year-old hypertensive woman had a cerebral vascular accident, or what was thought to be an ischemic cerebral vascular accident. She had a past history of

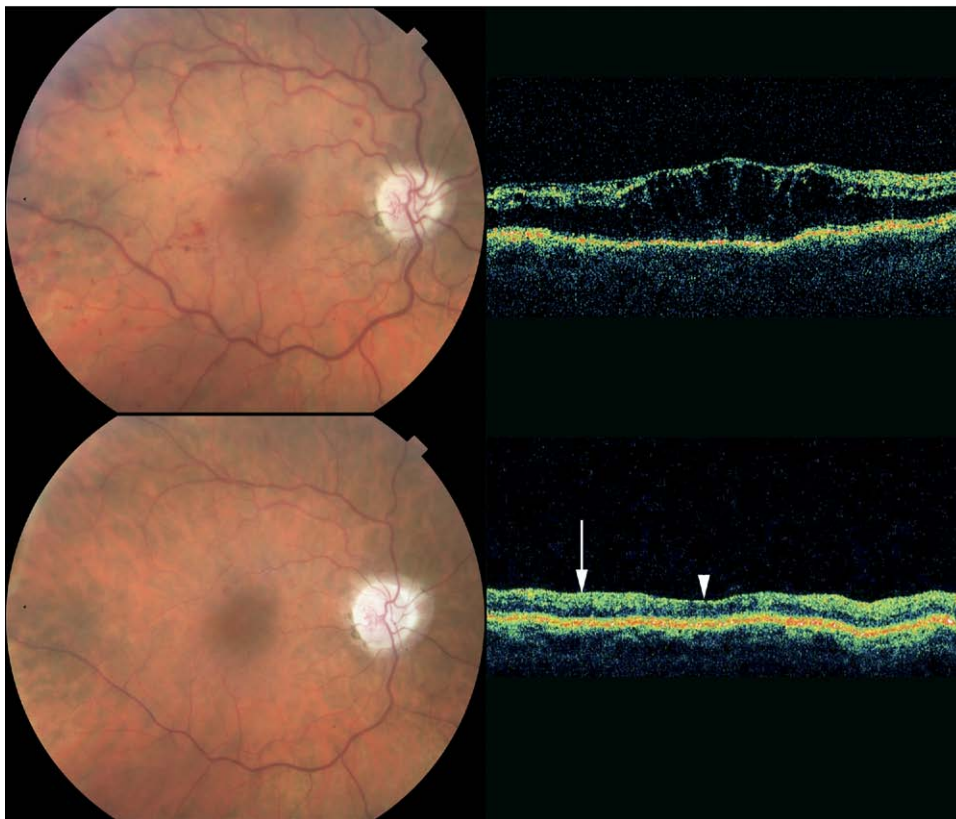


FIGURE 5. Images obtained from a 74-year-old man with CRVO 35 weeks before entry to the study. In that period, he received five injections of bevacizumab with a dramatic improvement in retinal appearance. However he continued to have macular edema, dot hemorrhages in the retina, and moderate optic atrophy. (Top left) Fundus photograph showing the dot hemorrhages in the retina. (Top right) OCT images showing the macular edema. (Bottom left) Fundus photograph obtained after one year in the study showing that the patient had resolution of the venous dilation and intraretinal hemorrhage. (Bottom right) OCT images showing that the macular edema resolved. Note the retinal atrophy, most markedly seen involving the inner retina (arrow) of the parafoveal macula, which ordinarily is much thicker than the fovea itself (arrowhead). The patient's VA improved 25 letters.

transient unilateral weakness before entry in the study and was evaluated with computed tomography. No abnormalities were seen and the patient was thought to have had a transient ischemic attack. After the fourth month of follow-up while enrolled in this study, she had an episode of mild drooping of the corner of her mouth and weakness in her arm that lasted a few minutes. She underwent a computed tomography evaluation that found no abnormality, and she was discharged with the diagnosis of a transient ischemic attack. However, a magnetic resonance imaging scan performed as an outpatient found an infarct. She was discovered to have an ipsilateral redundant loop in her carotid artery, but did not have any alteration in arterial diameter. The patient had no observable sequela from her stroke.

A 76-year-old male had a baseline VA of 53 letters and a baseline foveal thickness of 390 μm . Before entry into the study, he had undergone 10 injections of bevacizumab with partial resolution of his macular edema. He received two injections of ranibizumab in the study and had an increase in his VA to 60 letters and a decrease in macular thickness to 158 μm . However, he reported new-onset

distortion and was seen to have typical findings of focal vitreomacular traction syndrome during OCT examination. The patient underwent an uncomplicated vitrectomy with removal of the traction and removal of his internal limiting membrane. Because of the vitrectomy, he was exited from the study. Thereafter, he was treated using similar criteria to the study protocol, but with injections of bevacizumab. Curiously, over the course of the following year, the patient required only two bevacizumab injections.

DISCUSSION

THIS STUDY OF INTRAVITREAL RANIBIZUMAB FOR CRVO found an improvement in VA that began less than one week after the first injection and continued to show improvement after additional injections over the following year of follow-up. The patients showed a significant improvement in VA, with 94% having stabilization or improvement in acuity at one year. There was a reduction in macular edema, but the amount of change in macular edema was not correlated with the amount of change in VA.

Two patients had noteworthy side effects. In one patient with a previously unknown carotid artery abnormality but a past history of transient ischemic attack, what was thought to be another transient ischemic attack took place while the patient was participating in the study. A computed tomography scan obtained after each event showed no abnormality, but after the second transient ischemic attack, the patient underwent magnetic resonance imaging and magnetic resonance angiography, which indicated an infarct, probably of recent origin ipsilateral to a carotid artery abnormality. A potential concern with using any anti-VEGF agent is the theoretical increase in arterial thromboembolic events. A review of Medicare standard analytic files for patients with new-onset age-related macular degeneration before the advent of anti-VEGF therapy found that patients with past history of arterial thromboembolic events had an annual prevalence rate of 7.4% for myocardial infarction and 35.1% for inpatient ischemic stroke,¹⁵ implying that these patients have a high underlying risk for an arterial thromboembolic event. Although the rates for patients with age-related macular degeneration may be different than those with CRVO, a CRVO can be considered an ischemic event affecting the central nervous system, or at least a structure derived from the central nervous system. The second complication was the development of vitreomacular traction in a patient who had 10 previous bevacizumab injections and two injections of ranibizumab. Vitreomacular traction is a rare complication of CRVO¹⁶ and is associated more frequently with branch retinal vein occlusion.^{17–19} This patient underwent vitrectomy with internal limiting membrane removal and thereafter seemed to require less frequent anti-VEGF injections, albeit with a different agent. Vitrectomy increases the oxygen concentration at the level of the retina,²⁰ potentially reducing the stimulus for VEGF production.

In this series, blocking intraocular VEGF seemed to result in improved VA in patients with CRVO. Previous authors have classified CRVO as being ischemic or non-ischemic²¹ or, in the CRVO Study, as perfused vs nonperfused (with indeterminate eyes not being immediately classifiable).^{22,23} The CRVO Study used FA evidence of areas of absent flow to define nonperfusion, principally to create a method to predict those patients in whom iris neovascularization would develop. Nonperfused eyes were found to have a greater risk for iris neovascularization. More recent studies using primate eyes found that intravitreal VEGF injections produce findings that emulate CRVO, including areas of nonperfusion.^{6,24} Histopathologic analysis of the injected eyes showed endothelial cell proliferation occurring in capillaries to the point where the entire capillary was occluded. Vascular endothelial proliferation occurred within venules leading to obstruction, and the regions drained by these venules were seen to have capillary nonperfusion during FA.²⁴ It is likely that what appears as a nonperfused CRVO in humans is more related to the effects of VEGF and not something intrinsically

specific to occlusion of the central retinal vein. It is possible that anti-VEGF agents may prevent or reverse the excessive intravascular proliferation of vascular endothelial cells. It is not logical to call an acute condition nonischemic when it was produced by a vascular occlusion that causes VEGF secretion from the affected tissue. CRVOs likely exist in a continuum from mild to severe, with the resultant secretion of VEGF from the retina increasing with worsening of the blood flow. At very high levels of VEGF, decompensation of the retinal vasculature from intravascular proliferation of vascular endothelial cells, as was seen in the primate experiments, creates a self-reinforcing cycle of decompensation.

Intravitreal administration of anti-VEGF agents reduces tissue effects of VEGF, but does not necessarily address the underlying factors that lead to the increased VEGF in the first place. The arm-to-early arterial filling time was prolonged in the patients at presentation (Figure 3). One possible explanation is that low flow and increased hydrostatic pressure within the venules in turn caused a general slowing of the arterial inflow. However, after one year of receiving intravitreal ranibizumab with near normalization of the retinal thickness, retinal appearance, and improvement in VA, the arm-to-early arterial filling time showed no change (Figures 3 and 4). This finding implies that the arterial supply into these eyes was compromised. Reduction of venous outflow with simple ligation of the vein in primates did not produce a picture consistent with severe CRVO; to produce severe CRVO, simultaneous compromise in arterial flow was required.²⁵

It is likely that poor arterial perfusion of the retina sets the stage for the manifestations we ascribe to a CRVO, which are mediated to a large part by VEGF. Inhibition of VEGF seems to reverse to pathologic decompensation within the retina, but is there a cost to the retina for this type of treatment? VEGF has been found to be an important survival factor for retinal neurons and is a critical neuroprotectant.²⁶ Intuitively, it may seem that in this situation a nearly complete suppression of VEGF-mediated effects by ranibizumab may be undesirable. However in our series, slightly more than half of the patients previously had undergone treatment with bevacizumab, an agent that may not block the effects of VEGF as well as ranibizumab, and these patients showed the same magnitude of improvement in vision as those not treated with prior bevacizumab (Figure 5). It is possible that withdrawal of VEGF and its cell survival and neuroprotective effects allow marginally oxygenated neurons actually to die, resulting in a state where the retina overall requires less oxygenation. The metabolic and oxygen demands of the remaining cells are more closely matched with what is available from the retinal circulation. However, the patients in the present study still required frequent injections, indicating there was an unresolved perfusion deficit. This raises the possibility that treating patients with ranibizumab may stabilize the retina to the extent that other procedures such as vitrectomy may have a favorable long-term effect.

This series, although prospective, has a number of potential defects. The sample size was small, there was no control group, the investigators and patients were not masked, and several patients exited early from the study. Each of these factors limits the generalizability of the study. The use of ranibizumab in CRVO currently is being investigated in a randomized trial. The present study found that patients with CRVO showed a significant and sustainable improvement in VA when treated with intravitreal ranibizumab following a set of criteria that called for treatment if any aspect of CRVO was present including edema, as well as the presence of intraretinal hemorrhage.

This strategy was aimed at not solely treating macular edema. The strategy resulted in frequent injections over the year and resulted in a demonstrable improvement in vision. Of interest is that the VA at one month was not predictive of the one-year outcome, so a single injection followed by a wait-and-see approach is likely to be a suboptimal strategy. It may be possible that the best strategy is a recurrent periodic injection given at intervals found to prevent any recrudescence of retinal pathologic features, much the same as the strategy used in the treat-and-extend approach as has been described for choroidal neovascularization.²⁷

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