INTRAVITREAL BEVACIZUMAB (AVASTIN) TREATMENT OF MACULAR EDEMA IN CENTRAL RETINAL VEIN OCCLUSION

A Short-Term Study

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Purpose: To report the short term anatomic and visual acuity response after intravitreal injection of bevacizumab (Avastin, Genentech) in patients with macular edema due to central retinal vein occlusion (CRVO).

Methods: The authors conducted a retrospective study of patients with macular edema due to CRVO who were treated with at least one intravitreal injection of bevacizumab 1.25 mg in 0.05 mL. Patients underwent Snellen visual acuity testing, optical coherence tomography (OCT) imaging, and ophthalmoscopic examination at baseline and follow-up visits.

Results: There were 16 eyes of 15 consecutive patients with a mean age of 76.1 years (SD 9.8 years). Intravitreal triamcinolone had been previously administered to 9 patients, but all of these patients either had no improvement or had excessive intraocular pressure caused by the triamcinolone. The patients received a mean of 2.8 injections of bevacizumab per eye. No adverse events were observed, including endophthalmitis, clinically evident inflammation, increased intraocular pressure, retinal tears, retinal detachment, or thromboembolic events in any patient. The mean central macular thickness at baseline was 887 μm and decreased to a mean of 372 μm at month 1 ($P < 0.001$). The mean baseline acuity was 20/600 (logMAR = 1.48) and the mean acuity at month 1 was 20/200 (logMAR = 1.05), a difference that was highly significant ($P = 0.001$). At last follow-up, a mean of 3 months after the first injection, the mean visual acuity was 20/138 (logMAR = 0.84), which was significantly better than baseline ($P < 0.001$). Visual acuity improvement, defined as a halving of the visual angle, was seen in 14 of the 16 eyes.

Conclusion: Initial treatment results of patients with macular edema secondary to CRVO did not reveal any short-term safety concerns. Intravitreal bevacizumab resulted in a significant decrease in macular edema and improvement in visual acuity. The number of patients in this pilot study was limited and the follow-up is too short to make any specific treatment recommendations, but the favorable short-term results suggest further study is needed.

RETINA 26:279–284, 2006

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The authors have no proprietary interests in this study.

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Central retinal vein occlusion (CRVO) causes decreased tissue perfusion and increased hydrostatic pressure within the involved segments as a consequence of the vascular obstruction. This leads to a constellation of findings including intraretinal hemorrhage, exudation of fluid, varying levels of ischemia,[1] and the possible development of neovascular complications such as rubeosis iridis and neovascular glaucoma. There is no proven therapy for visual decline associated with CRVO. Intravitreal injection of triamcinolone has caused a marked reduction of macular edema in some patients and has been accompanied by reduction in venous dilation, intraretinal hemorrhages, and optic disk swelling.[2–7] The visual acuity and central macular thickness appear to improve after intravitreal triamcinolone, but the potential benefits need to be balanced with the high risk of developing increased intraocular pressure[8–10] and the near certainty of cataract formation,[11] especially if repeated injections are required.

Retinal vein occlusion is associated with increased intravitreal levels of vascular endothelial growth factor (VEGF),[12] particularly in cases complicated by neovascularization.[13] Eyes with CRVO show evidence of intraretinal VEGF mRNA expression.[14] Inhibition of VEGF by antisense oligodeoxynucleotide[15] or anti-VEGF monoclonal antibody[16] resulted in reduction or complete prevention of iris neovascularization in animal models of CRVO. Since intraocular injection of VEGF causes retinal microvascular abnormalities and retinal ischemia,[17] and since retinal vein occlusion itself causes increased intraocular VEGF that varies with disease severity,[18] inhibition of VEGF in human CRVO may have therapeutic potential. A recombinant humanized monoclonal antibody directed against VEGF is available (bevacizumab, Avastin, Genentech) for cancer therapy.[19] Intravitreal bevacizumab in humans has been previously described on an anecdotal basis for the treatment of CRVO and age- related macular degeneration.[20,21] We have offered intravitreal injection of bevacizumab to patients with CRVO with the hopes of decreasing the morbidity of CRVO. This report describes the early response that a series of patients with CRVO had to intravitreal bevacizumab.

Methods

We conducted a retrospective study of 16 eyes of 15 patients with macular edema due to CRVO who were given off-label intravitreal bevacizumab. Informed consent was obtained from all patients. This study had Institutional Research Board approval. Each patient underwent best-corrected distance visual acuity measurement with Snellen chart, and ophthalmic examination including slit lamp biomicroscopy. Baseline central retinal thickness was measured by optical coherence tomography (OCT) using 5-mm raster line scans. Thirteen of the 16 eyes had a baseline fluorescein angiogram. The intravitreal dosage of bevacizumab was 1.25 mcg/0.05 cc. All injections were performed in the usual sterile fashion[22] and prophylactic topical antibiotics were given for 2 days postinjection. The patients were examined at 1 week and 1 month after the first injection. One month after initial injection, reinjection was performed at the discretion of the investigator. Repeat OCT was performed at 1-month intervals.

Fluorescein angiograms were obtained by injection of 2 mL of 25% sodium fluorescein solution in the antecubital vein. The time for the dye to first appear in the arterioles until the end of the laminar filling stage was recorded as the arterial venous filling time. Eyes were considered ischemic by fluorescein angiographic criteria if they had no observable neovascularization of the iris and had 10 or more disk areas of nonperfusion.

Statistical analysis for descriptive statistics was performed using SPSS statistical software (version 12.0; SPSS Inc., Chicago, IL). The visual acuity was converted to logMAR before analysis. The data obtained were analyzed with frequency and descriptive statistics. Categorical data were analyzed with chi-square testing unless an expected cell count was less than 5 in which Fisher exact test was used. Decrease in visual acuity was considered to have occurred if there was a doubling of the visual angle. If the visual angle at follow-up was one-half or less than the pretreatment value the acuity was considered to be improved. Any outcome in between was considered to be the same as the pretreatment value. The main outcome measurements were visual acuity and central retinal thickness measured by OCT.

Results

Baseline Characteristics

A total of 16 eyes from 15 patients were reviewed. The mean follow-up time was 90 days (range 34–133). Of the 15 patients, 14 (93%) had hypertension and 1 (6.7%) had diabetes. Interestingly, a large proportion of the patients were being treated with some form of anticoagulation: 8 (53%) took aspirin, 2 (13.3%) took warfarin, and 1 (6.7%) clopidogrel. Of the 15 treated eyes, 9 had prior intravitreal triamcinolone acetonide and 3 had more than five corticosteroid injections. All of these eyes were considered

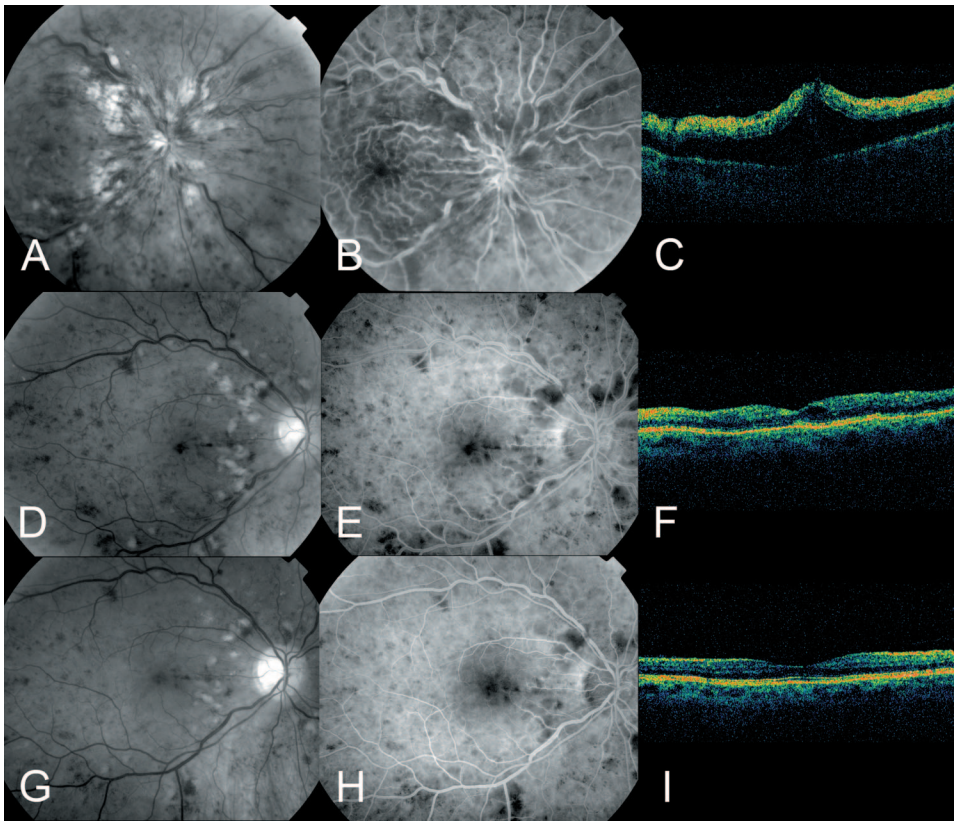

Fig. 1. **A,** Pretreatment red-free photograph showing multiple cotton-wool spots, swelling of the nerve, intraretinal hemorrhages, and dilated and tortuous vein. **B,** The fluorescein angiogram shows remarkable distension of the retinal vessels, areas of nonperfusion, swelling of the nerve, and intraretinal hemorrhages. **C,** Optical coherence tomography (OCT) shows massive macular edema with poor visualization of the retinal pigment epithelium due to shadowing. The visual acuity was 10/400. One month after the first intravitreal injection of bevacizumab the visual acuity was 20/60. The red-free photograph and fluorescein angiogram (**D** and **E**) shows resolution of the optic nerve head edema, reduction in the cotton-wool spot size, and some resorption of intraretinal hemorrhage. There was a small hemorrhage remaining in the fovea. The OCT scan shows marked improvement in the foveal thickness and contour (**F**). One month after the second injection the patient had further resorption of intraretinal hemorrhage and an improved appearance of the retinal vessels (**G** and **H**). The OCT at that time revealed a normal appearing macula (**I**).

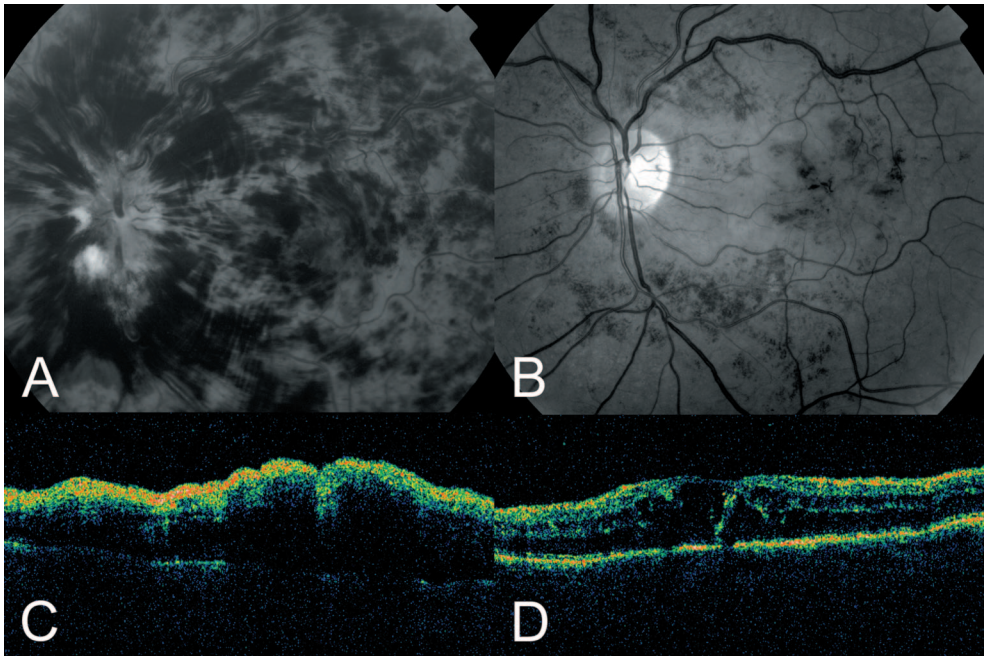

Fig. 2. **A,** The red-free photograph shows considerable optic nerve swelling, cotton-wool spots, and dense intraretinal hemorrhage. The visual acuity was 5/400. **B,** Three months after presentation, and 5 weeks after his second injection, there was resolution of the edema of the optic nerve head and resorption of most of the intraretinal hemorrhage. The visual acuity was 20/100. **C,** At baseline the patient had a huge amount of edema and blood within the macula. **D,** Optical coherence tomography scan obtained the same day as **B** shows the presence of some intraretinal edema. The patient was reinjected with 1.25 mg of bevacizumab.

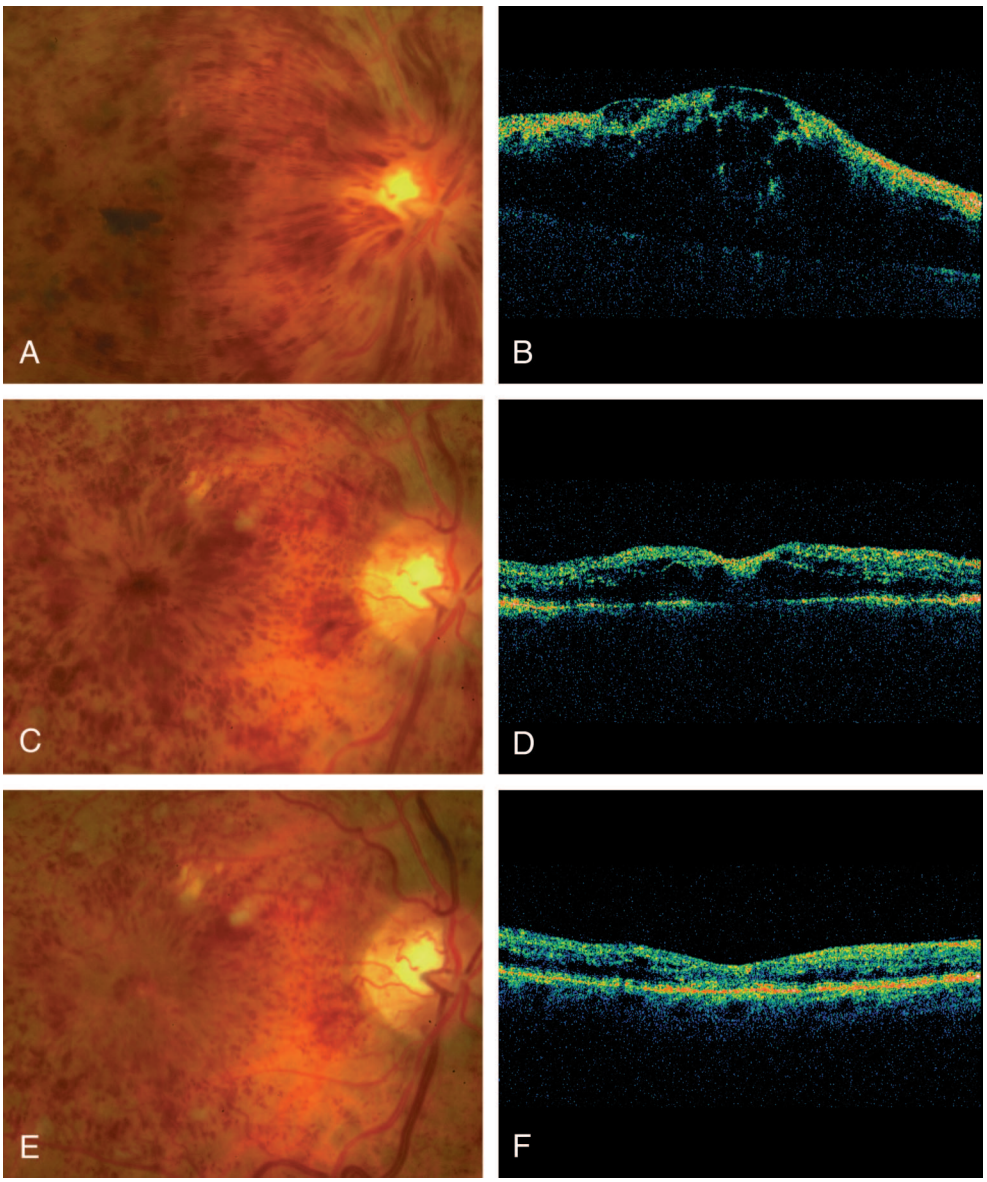

Fig. 3. Successive photographs and optical coherence tomography scans taken at baseline and 1 and 2 months after presentation. The patient was reinjected at 1 month after presentation with 1.25 mg of bevacizumab. **A, B,** The patient initially had a visual acuity of 10/400, swelling of the nerve and macula, dilated retinal veins, and a collection of blood in the fovea. **C, D,** One month after presentation the visual acuity was unchanged, but the fundus picture and optical coherence tomography results looked improved. Note the hemorrhage in the fovea. **E, F,** Two months after presentation the patient showed further resolution of the nerve swelling, dilation of the veins, and macular edema. Note the clearing of the foveal blood. There were resolving cotton-wool spots seen in areas previously covered with blood. The visual acuity was 20/100.

corticosteroid treatment failures in that all of these patients had either no improvement in visual acuity or developed intraocular pressure management problems following intravitreal triamcinolone. One eye had rubeosis. Of the 13 eyes without rubeosis 5 were ischemic according to the Central Retinal Vein Occlusion Study Group (CVOS) definition of greater than 10 disk areas of nonperfusion[22] and 2 were indeterminate. The baseline characteristics included a mean visual acuity of nearly 20/600 (logMAR = 1.48 ± 0.48), mean foveal thickness of 887 (± 251) μm, mean arterial venous filling time of 62.4 (±9.3) seconds, and mean intraocular pressure of 18 (± 2.4) mmHg. All of the eyes had cystoid macular edema by OCT examination at baseline.

One-Month Outcomes

Statistically significant changes in visual acuity and foveal thickness were observed at month 1 follow-up. Visual acuity at 1 month improved to a mean of 20/200 (logMAR = 1.05 ± 0.49), a difference from baseline that was highly significant ($P = 0.001$, paired samples *t* test). The change in logMAR from baseline was somewhat more in patients who did not have previous triamcinolone. Mean post-treatment central foveal thickness was 372 (±256) μm ($P < 0.001$, paired samples *t* test). The proportion change in macular thickness as compared with baseline measurements showed no significant difference in patients who did or did not have previous intravitreal injection

of triamcinolone ($P = 0.99$, paired samples t test). The mean intraocular pressure was 16.4 mmHg. The mean arterial venous filling time decreased to 20.9 seconds, a difference from baseline that was not statistically significant ($P = 0.6$). We observed a reduction of neovascularization in the eye presented with rubeosis.

Last Follow-Up Outcomes

At the last post-treatment visit, which occurred at a mean of 3 months after the start of treatment, the mean visual acuity was 20/138 (logMAR = 0.84 ± 0.53). Of the 16 eyes, 14 (87.5%) had better visual acuity, defined as halving of the visual angle as compared with baseline, and 2 eyes (12.5%) had no change. During follow-up, no adverse events were noted. A total of 45 injections of bevacizumab were performed at the end of the follow-up period. There were no cases of endophthalmitis, clinically evident inflammation, increased intraocular pressure, retinal tear, retinal detachment, or thromboembolic events.

Discussion

Consecutive eyes with CRVO treated with intravitreal bevacizumab in this retrospective study demonstrated both anatomic and functional improvement. Patients showed a marked decrease in macular edema and an improvement in visual acuity, even though most previously had a poor response to intravitreal triamcinolone. We did not find any observable side effects with intravitreal bevacizumab such as inflammation, infection, increased intraocular pressure, retinal tear, or detachment. Although it had been practice in the past to grade the severity of CRVOs into ischemic and nonischemic based on fluorescein angiographic or other criteria,[1] the logic and utility of this practice is brought to question by the results of this study. Among the 13 eyes without rubeosis, only 5 would have been graded as being ischemic. However nearly every eye showed some anatomic or visual acuity improvement, with the majority showing at least a halving of their visual angle through the use of an anti-VEGF antibody. Since the release of VEGF in CRVO is thought to be stimulated by ischemia, it would appear that all eyes with CRVO are ischemic to some degree. The short-term results of this study, which was nonrandomized, uncontrolled, and retrospective, preclude any estimation of the long-term efficacy or safety of intravitreal bevacizumab. However, the results were very promising and show the need for further investigation (Figures 1–3).

Key words: bevacizumab, central retinal vein occlusion, macular edema, vascular endothelial growth factor, fluorescein angiography.

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