Bevacizumab for Macular Edema in Central Retinal Vein Occlusion: A Prospective, Randomized, Double-Masked Clinical Study

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Purpose: To evaluate the efficacy of intraocular injections with bevacizumab in patients with macular edema (ME) secondary to central retinal vein occlusion (CRVO).

Design: Prospective, randomized, sham injection-controlled, double-masked clinical trial.

Participants: Sixty patients with ME secondary to CRVO.

Methods: At baseline, patients were randomized 1:1 to receive intraocular injections of bevacizumab or sham injections every 6 weeks for 6 months.

Main Outcome Measures: The primary outcome measure was the proportion of patients gaining at least 15 letters at 6 months. Secondary outcome measures included mean change from baseline best-corrected visual acuity (BCVA), foveal thickness, and neovascular glaucoma.

Results: At the end of follow-up, 18 of 30 patients (60.0%) in the study group had gained ≥15 letters compared with 6 of 30 patients (20.0%) in the control group ($P=0.003$). The BCVA improved by 14.1 letters at 24 weeks compared with a decrease of 2.0 letters in the control group ($P < 0.003$). The mean decrease in central retinal thickness (CRT) was significantly greater in the study group (426 μm) than in the control group (102 μm) at all time points up to week 24 ($P < 0.001$). No residual edema, defined as CRT <300 μm at 24 weeks, was found in 26 of 30 patients (86.7%) in the treatment group compared with 6 of 30 patients (20%) in the control group ($P < 0.001$). In the sham group, 5 of 30 patients (16.7%) had developed iris rubeosis at week 24. No patients in the study group had rubeosis at week 24 ($P=0.052$). There were no events of endophthalmitis, retinal tear, or retinal detachment during the 24-week treatment period. No serious non-ocular adverse events were reported.

Conclusions: Intraocular injections of bevacizumab given every 6 weeks for 6 months improve visual acuity (VA) and reduce ME significantly compared with sham.

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Retinal vein occlusion is the second most common retinal vascular disease after diabetic retinopathy and is associated with a severe decrease in visual acuity (VA).[1,2] In central retinal vein occlusion (CRVO), the most common vision-threatening complications are retinal ischemia and macular edema (ME). In the past, many different treatment modalities have been suggested, including laser photocoagulation, vitrectomy, laser-induced chorioretinal anastomosis, radial optic neurotomy, and intravitreal tissue plasminogen activator.[3–9] None of these treatments have shown sustained visual improvement. However, in 2 recent studies using intravitreal steroids, the Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) study and the Global Evaluation of Implantable Dexamethasone in Retinal Vein Occlusion with Macular Edema (GENEVA) study, a significant treatment benefit was demonstrated. The SCORE study showed that intravitreal triamcinolone was superior to observation only, although there was no net visual improvement and the study group showed an increased risk of developing cataract, steroid-induced ocular hypertension, and intractable glaucoma.[10] The GENEVA study showed that intravitreal dexamethasone prepared in a slow-release copolymer (Ozurdex, Allergan Inc., Irvine, CA) improved vision significantly and decreased the risk for vision loss. Treated patients developed ocular hypertension significantly more often than patients in the sham group.[11]

The functional and structural changes resulting from the venous thrombus formation eventually lead to the development of retinal hypoxia with upregulation and release of vascular endothelial growth factor-A (VEGF-A). The intravitreal level of VEGF in patients with CRVO is the highest of those found in any retinal vascular disease, and a correlation has been found between VEGF concentrations at the onset of neovascularization and the extent of retinal capillary nonperfusion and vascular permeability.[12,13] Vascular endothelial growth factor-A increases vascular permeability and has been implicated as an important factor responsible for ME in patients with CRVO. Targeting VEGF-A is consequently an attractive treatment strategy for these patients. Indeed, in the Treatment of Macular Edema after Central Retinal Vein Occlusion (CRUISE) study, intravitreal ranibizumab (Lucentis [Genentech Inc, South San Fran-

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cisco, CA] anti-VEGF Fab) improved vision significantly compared with sham, with approximately half the patients gaining ≥3 Early Treatment Diabetic Retinopathy Study (ETDRS) lines.[14] Bevacizumab (Avastin [Genentech Inc] anti-VEGF IgG) has shown improvements in VA and ME after intravitreal treatment, although no prospective randomized sham controlled study has been conducted.[15–17] The present prospective, double-blind, randomized, controlled study investigated whether repeated intravitreal bevacizumab (IVB) injections can improve VA compared with sham-treated control patients with ME secondary to CRVO.

Patients and Methods

This randomized prospective study was performed at St. Eriks Eye Hospital in Stockholm, Sweden. The study adhered to the tenets of the Declaration of Helsinki. The protocol was approved by the local ethics committee and the Swedish Medical Products Agency. Each subject gave written informed consent to participate in the study. The study is listed on www.clinicaltrials.gov, under identifier NCT00906685.

Study Population

From April 2009 to December 2010, 60 eyes of 60 patients with CRVO were consecutively enrolled. These patients comprised the intent-to-treat population, in whom the last observation carried forward method was used for missing data for all efficacy parameters. One patient in the bevacizumab group had missing data for VA and OCT thickness, and 2 patients in the sham group had missing data for OCT thickness. No other missing data were present. The main study inclusion and exclusion criteria are summarized in Table 1.

Study Design

After eligibility was determined and informed consent was obtained, each study participant was randomly assigned with equal probability to IVB injections (study group) or sham injections (control group). Randomization was done at the day of the first injection by sealed envelopes drawn by staff not involved in patient treatment or follow-up. Each patient received 4 injections (bevacizumab or sham) one, every 6 weeks. The total follow-up period was 24 weeks. Study patients were masked to the treatment given. Staff performing VA testing, optical coherence tomography (OCT), fundus photographs, and follow-up investigators were masked to treatment group.

Table 1. Main Inclusion/Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
CRVO with a duration of 6 months or less	CRVO with neovascularisation
Best corrected visual acuity (BCVA) between 15–65 ETDRS letters (Snellen equivalent approximately 20/50 to 20/500)	Any previous treatment for CRVO
Mean central subfield thickness ≥ 300μm as measured by OCT (Cirrus OCT)	Intraocular surgery during the previous 3 months Vascular retinopathy of other causes Glaucoma with advanced visual field defect or uncontrolled ocular hypertension >25mmHg despite full therapy Myocardial infarction or stroke during the last 12 months

CRVO = central retinal vein occlusion, ETDRS = Early Treatment Diabetic Retinopathy Study, OCT = optical coherence tomography.

Outcome Measures

The primary outcome measure was the proportion of patients gaining ≥15 ETDRS letters at 6 months. The secondary outcome measures were change in best-corrected visual acuity (BCVA), change in foveal thickness as measured by OCT, and the number of patients with neovascular glaucoma defined as increased intraocular pressure caused by new vessels forming in the angle as diagnosed by gonioscopy.

Examination Procedure

At baseline and at each follow-up visit, BCVA was measured at a distance of 4 m (or at 1 m if needed) by a certified tester using an ETDRS chart. Gonioscopy was performed before dilation at all visits. After dilation, OCT images were obtained by a certified technician using the Zeiss Cirrus OCT machine (Carl Zeiss Meditec, Inc, Dublin, CA). The scans included a 5 raster scan pattern and the cube for quantitative measuring. If the automated thickness value was determined to be inaccurate, central retinal thickness (CRT) was measured manually. A fluorescein angiogram and color and red-free photographs were performed at baseline and at week 24. At each follow-up visit, a full slit-lamp examination was done with a dilated fundus examination. The intraocular pressure was measured with a Goldmann tonometer.

Treatment Procedure

All eyes were treated with topical antibiotics 30 minutes before injection (fucidinic acid 1%). The eyelids and periorbital area were scrubbed with chlorhexidine solution (5%) followed by irrigation of the conjunctiva with chlorhexidine solution (0.5%). A sterile drape was put on, and a sterile speculum was placed between the lids. Topical anesthesia was obtained by 1% tetracaine and with a sterile cotton swab soaked in 1% tetracaine applied temperoinferiorly at the site designated for injection. Intravitreal bevacizumab was prepared under sterile conditions at the hospital pharmacy by dividing a vial of bevacizumab (Avastin) into small vials for each patient. Patients randomized to the study group received an intravitreal injection of 1.25 mg (0.05 ml) bevacizumab via the pars plana using a tuberculin syringe with a 30-gauge needle. Patients in the control group received a sham injection by pressing a syringe without a needle to the globe.

Power Calculation and Statistical Analysis

The primary hypothesis was based on a difference between the treatment groups in the proportion of patients achieving the main outcome measure. We assumed that 35% of the patients treated with bevacizumab and 5% of the sham-treated patients would achieve the primary end point (gain of at least 15 ETDRS letters). With a statistical power of 80% and the level of statistical significance set at $P < 0.05$, we estimated that a minimum of 24 patients would be required (MedCalc Software, Mariakerke, Belgium). For statistical analyses, the independent Student t test and the Fisher

Table 2. Patient Demographics and Baseline Ocular Characteristics

Parameter	Sham $n = 30$	Bevacizumab $n = 30$	All
Age (yrs ± SD)	70.4±10.4	70.6±12.6	70.5±12.6
Gender ratio M:F n (%)	17:13 (57:43)	19:11 (63:37)	36:24 (60:40)
Time from diagnosis to inclusion (wks ± SD)	9.4±6.5	8.3±4.8	8.8±5.7
<90 days n (%)	22 (73.3)	21 (70)	43/60 (71.7)
>90 days n (%)	8 (26.7)	9 (30)	17/60 (28.3)
BCVA (ETDRS letters ± SD)	43.9±16.0	44.4±15.3	44.1±15.5
BCVA distribution n (%)			
<34	10 (33.3)	9 (30)	19 (31.7)
>34	20 (66.7)	21 (70)	41 (58.3)
CRT (μm ± SD)	729±195	712±330	721±269
Hypertension n (%)	16 (53.3)	13 (43.3)	29 (48.3)
Diabetes mellitus n (%)	3 (10)	1 (3.3)	4 (6.7)

BCVA = best corrected visual acuity; CRT = central retinal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; M:F = male:female; SD = standard deviation.
P value was nonsignificant between treatment groups for all parameters.

exact test (to compare differences in distributions between the groups) were used.

Results

Sixty eyes of 60 patients were assigned randomly to IVB (30 eyes) or sham injections (30 eyes). Demographic and baseline characteristics are listed in Table 2. There were no statistically significant differences between the groups. The mean age was 70.5 years (range 52–93 years). The majority of included eyes (36/60 eyes [60.0%]) were from male patients. The mean VA at baseline was 44.1 ETDRS letters (range, 15–65) (Snellen equivalent 20/125, range, 20/50–20/500). The mean duration of symptoms before the first injection was 8.8 weeks (range 1–25 weeks). The average baseline CRT as measured by OCT was 721 μm (range 349–1371 μm).

Visual Acuity

At 6 weeks there was an improvement of VA compared with baseline by a mean of 7.5 letters in the study group (Fig 1). The VA further improved by 11.4 letters at 12 weeks, 13.9 letters at 18 weeks, and 14.1 letters at 24 weeks (Fig 1). In the control group, the VA decreased by 0.3, 3.9, 3.2, and 2.0 letters at 6, 12, 18, and 24 weeks, respectively. The difference in VA between the treatment groups was statistically significant from week 12 and beyond ($P < 0.01$). At the end of follow-up, 18 of 30 patients (60.0%) in the study group had gained ≥15 letters compared with 6 of 30 patients (20.0%) in the control group ($P=0.003$). In the control group, 7 of 30 patients (23.3%) lost >15 ETDRS letters compared with 2 of 30 patients (6.7%) in the study group ($P = 0.146$). Snellen BCVA equivalent of ≤20/200 is considered a poor visual outcome. In the study group, 4 of 30 patients (13.3%) had this outcome compared with 11 of 30 patients (36.7%) in the control group ($P = 0.072$). A subgroup analysis of patients with disease duration more or less than 90 days was performed. Patients with a disease duration <90 days improved 18.7 letters ($P < 0.001$) compared with patients with disease duration >90 days, who gained 9.8 letters ($P = 0.039$) (Fig 2).

Anatomic Outcomes at 24 Weeks

Central Retinal Thickness. The mean decrease in CRT was significantly greater in the study group (426 μm) than in the

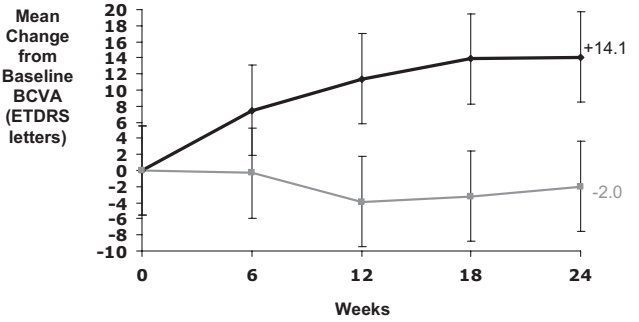

Figure 1. Mean change from study eye baseline BCVA over time to month 6. The difference in BCVA between the treatment groups was statistically significant from week 12 ($P < 0.01$) onward. The last observation carried forward method was used to compute missing data. BCVA = best corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study. p<0.003; —◆—Bevacizumab; —■—Sham.

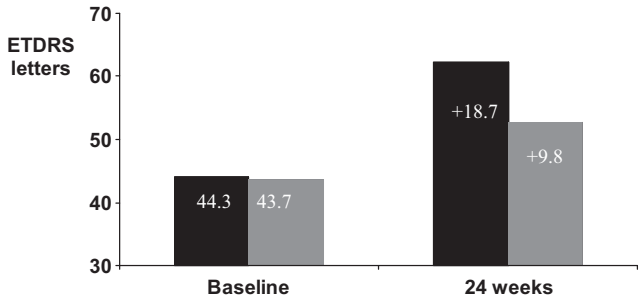

Figure 2. Change in BCVA (ETDRS letters) according to disease duration in patients treated with bevacizumab. Patients with a disease duration <90 days improved from Snellen equivalent ~20/126 to 20/50 significantly more ($P < 0.001$) than patients with disease duration >90 days (20/126 to 20/80). ETDRS = Early Treatment Diabetic Retinopathy Study. ■ <90 days; □ >90 days.

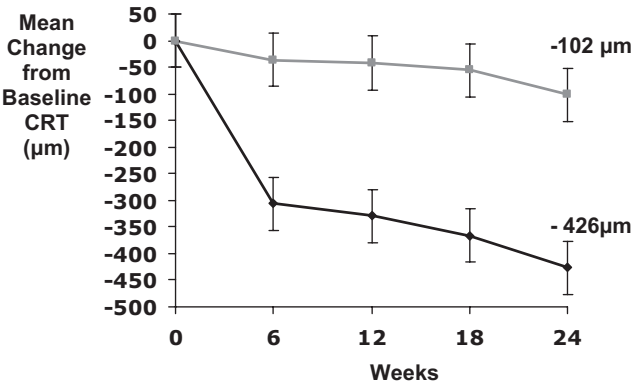

Figure 3. Mean change from baseline CRT over time to month 6. The mean decrease in CRT was significantly greater in the study group than in the control group at all time points up to week 24 ($P < 0.001$). The last observation carried forward method was used to compute missing data. CRT = central retinal thickness. p<0.001; —●—Bevacizumab; —■—Sham.

control group (102 μm) at all time points up to week 24 ($P < 0.001$) (Fig 3). No residual edema, defined as CRT <300 μm at 24 weeks, was found in 26 of 30 patients (86.7%) in the treatment group compared with 6 of 30 patients (20%) in the control group ($P < 0.001$).

Neovascularization. In the sham group, 5 of 30 patients (16.7%) had developed iris rubeosis at week 24. No patients in the study group had rubeosis at week 24 ($P = 0.052$). No significant difference was seen in the baseline BCVA in the control group for patients who later developed neovascularization. The baseline BCVA was 44.2 ETDRS letters for patients developing neovascularization compared with 43.9 ETDRS letters overall in the control group. Patients developing neovascularization lost 11.0 ETDRS letters compared with a loss of 2.0 ETDRS letters overall in the control group ($P = 0.228$).

Safety. There were no events of endophthalmitis, retinal tear, or retinal detachment during the 24-week treatment period. No serious non-ocular adverse events were reported.

Discussion

To the best of our knowledge, this is the first randomized prospective study on the efficacy of IVB for CRVO. Our study shows that IVB every 6 weeks for 6 months is superior to sham treatment. In the IVB-treated group, 60% of patients improved at least 3 ETDRS lines and gained a mean of 14.1 letters at 6 months. Thus, the primary end point of the study was met (i.e., a significantly higher proportion of patients gained >15 ETDRS letters after IVB treatment).

The present randomized controlled trial confirms results from recent case series showing a substantial improvement in the VA of patients with CRVO treated with IVB. However, these studies differ considerably in severity and disease duration, number of injections, and follow-up. In 2 studies, patients with CRVO had BCVA improved from 20/250 to 20/80[17] and from 20/100 to 20/50 at 12 months after IVB, respectively.[16] In our case study, after 4 IVB injections over 6 months, there was a marked visual improvement from logarithm of the minimum angle of resolution 0.86 to 0.48 (24 ETDRS letters).[15] The effect of bevacizumab is short, and it is likely that repeated injections are necessary to maintain visual recovery and will yield a better final outcome for at least as long as the disease exhibits signs of activity.[14] For this reason and in view of the positive experience from our pilot study, we chose to maintain a fixed dosing regimen in the present study.

Our results compare favorably to those of recent randomized studies on intravitreal ranibizumab (CRUISE study), triamcinolone (SCORE study), and dexamethasone implant (GENEVA study). In the CRUISE study, 48% of patients showed improved BCVA of at least 3 ETDRS lines and gained a mean of 14.9 letters after intravitreal injections of ranibizumab every 4 weeks for 6 months. The SCORE study showed a loss of 1.2 letters at 12 months in the group receiving 4 mg triamcinolone treatment. In the GENEVA study, a peak improvement in BCVA of 9.7 letters was seen at 60 days. Direct comparisons between studies should always be made with caution, and disease duration was different in these studies. Patients in the GENEVA study had a longer disease duration, with 84% of subjects treated more than 90 days after disease onset versus 30% in our study and 28% in the CRUISE study. This difference may explain less improvement in BCVA in the GENEVA study.[11,14] Indeed, our results show that patients with a disease duration <90 days improved 18.3 letters compared with 9.1 letters in patients with a disease duration >90 days. Moreover, the mean baseline ETDRS letter score was 44.1 in the present study compared with 48.1 in the CRUISE study.[14] Earlier studies have shown that subjects with a lower initial BCVA may improve more than patients with a better initial BCVA after treatment.[14] On the other hand, our study allowed inclusion of patients with more severe disease than previous prospective studies.[11,14] For instance, the presence of a relative afferent pupillary defect was not an exclusion criteria, and patients with a BCVA of at least 20/500 could be included in our study. In our study, the control group lost a mean of 2.0 letters at 6 months, which is comparable with the mean loss of 3.1 letters in the GENEVA study and the mean gain of 0.8 letters in the CRUISE study.

Earlier reports of the pharmacokinetics of intravitreal anti-VEGF agents in animal models suggest that bevacizumab has a longer intravitreal half-life than ranibizumab. In the rabbit eye, the vitreous half-life of intravitreal ranibizumab is 2.88 days versus 4.32 days for bevacizumab.[18] In humans, the vitreous half-life of ranibizumab and bevacizumab is approximately 10 days, suggesting that the duration of their therapeutic effects should not differ much.[19,20] In humans, there is also no clinical evidence that patients undergoing bevacizumab therapy for retinal disease require less frequent injections than patients receiving ranibizumab. Of note, we achieved the same visual improvement in response to IVB every 6 weeks as was obtained after ranibizumab every 4 weeks in the CRUISE study. As shown in our study, an injection schedule every 6 weeks seems to be reasonable, and even advantageous, by allowing fewer control visits. Thereby, intraocular trauma is reduced, the risk of inflammation and infections is decreased, and the burden

for patients and health care is alleviated. This may have an important logistic and economic impact.

Neovascular glaucoma is a feared complication to CRVO. The present study included patients with risk factors for developing this complication, for example, poor VA and severe ischemic changes. Indeed, 17% of patients in the sham group developed iris rubeosis and secondary glaucoma. In the treatment group, no patients developed these complications, supporting previous observations suggesting a potential protective effect of IVB. However, it is important to remember that we are changing the pathobiology of the disease by injecting anti-VEGF agents. It is possible that there may be a delay in the onset of neovascular complications, especially when the anti-VEGF agents are redrawn. This may necessitate a longer follow-up of these patients.

Sample size considerations are driven by efficacy considerations, safety considerations, or both. In this study, our sample size of 60 subjects, half exposed to drug, allowed us to determine that bevacizumab is effective compared with sham. We did not detect safety concerns. To detect unexpected severe adverse events that occur at a 1% rate would have required approximately 300 subjects exposed to drug. To detect an increase in a serious adverse event (e.g., myocardial infarction or stroke of 1% from 2% to 3%) would require a study with thousands of subjects.

In conclusion, the present study shows that IVB injections given every 6 weeks for 6 months improve vision and reduce ME significantly compared with sham. These results justify the use of IVB in patients with ME secondary to CRVO. A 52-week open-label extension of this study is ongoing and investigating whether the functional gains in the IVB group are maintained and whether a delay of 24 weeks in the sham group will affect treatment outcome.

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Footnotes and Financial Disclosures

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