Sustained Benefits from Ranibizumab for Macular Edema following Central Retinal Vein Occlusion: Twelve-Month Outcomes of a Phase III Study

Peter A. Campochiaro, MD,[1] David M. Brown, MD, FACS,[2] Carl C. Awh, MD,[3] S. Young Lee, MD,[4] Sarah Gray, PhD,[5] Namrata Saroj, OD,[5] Wendy Yee Murahashi, MD,[5] Roman G. Rubio, MD[5]

Purpose: Assess the 12-month efficacy and safety of intraocular injections of 0.3 mg or 0.5 mg ranibizumab in patients with macular edema after central retinal vein occlusion (CRVO).

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

Participants: We included 392 patients with macular edema after CRVO.

Methods: Eligible patients were randomized 1:1:1 to receive 6 monthly intraocular injections of 0.3 mg or 0.5 mg of ranibizumab or sham injections. After 6 months, all patients with BCVA ≤20/40 or central subfield thickness ≥250 μm could receive ranibizumab.

Main Outcome Measures: Mean change from baseline best-corrected visual acuity (BCVA) letter score at month 12, additional parameters of visual function, central foveal thickness (CFT), and other anatomic changes were assessed.

Results: Mean (95% confidence interval) change from baseline BCVA letter score at month 12 was 13.9 (11.2–16.5) and 13.9 (11.5–16.4) in the 0.3 mg and 0.5 mg groups, respectively, and 7.3 (4.5–10.0) in the sham/0.5 mg group ($P<0.001$ for each ranibizumab group vs. sham/0.5 mg). The percentage of patients who gained ≥15 letters from baseline BCVA at month 12 was 47.0% and 50.8% in the 0.3 mg and 0.5 mg groups, respectively, and 33.1% in the sham/0.5 mg group. On average, there was a marked reduction in CFT after the first as-needed injection of 0.5 mg ranibizumab in the sham/0.5 mg group to the level of the ranibizumab groups, which was sustained through month 12. No new ocular or nonocular safety events were identified.

Conclusions: On average, treatment with ranibizumab as needed during months 6 through 11 maintained the visual and anatomic benefits achieved by 6 monthly ranibizumab injections in patients with macular edema after CRVO, with low rates of ocular and nonocular safety events. After sham injections for 6 months, treatment with ranibizumab as needed for 6 months resulted in rapid reduction in CFT in the sham/0.5 mg group to a level similar to that in the 2 ranibizumab treatment groups and an improvement in BCVA, but not to the same level as that in the 2 ranibizumab groups. Intraocular injections of ranibizumab provide an effective treatment for macular edema after CRVO.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2011;118:2041–2049

Central retinal vein occlusion (CRVO) is an important cause of vision loss and is estimated to have a 15-year cumulative incidence of 0.5% in a population study based in Wisconsin[1] and to affect 0.4% of the population in Australia.[2] As the name indicates, the inciting event is thought to be thrombosis within the central retinal vein, and there is pathologic evidence to support that contention.[3] Occlusion of the major outflow channel of the retinal circulation markedly increases intraluminal venous pressure, resulting in hemorrhages and edema. Massive swelling within the retina also causes variable amounts of capillary closure in some, but not all, patients. Vision is reduced if there are hemorrhages and/or edema in the macula or if there is closure of a substantial proportion of the perifoveal capillaries, resulting in macular ischemia. Hemorrhages are gradually resorbed, leaving edema and/or ischemia in the macula as the major causes of reduced vision, with the former predominant in most patients.

Recent studies have demonstrated that, while increased venous pressure may be the precipitating event for hemorrhages and edema, increased production of vascular endothelial growth factor (VEGF) occurs early in the disease process and is a major contributor to macular edema.[4–6] Those studies were made possible by the development of ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA), a humanized, affinity-matured anti-VEGF anti-

ISSN 0161-6420/11/$–see front matter
doi:10.1016/j.ophtha.2011.02.038

body fragment that binds to and neutralizes all isoforms of VEGF-A and their biologically active degradation products. A small, interventional pilot study in patients with CRVO or branch retinal vein occlusion demonstrated that monthly injections of 0.3 mg or 0.5 mg ranibizumab for 3 months caused a marked reduction in macular edema and a mean improvement in best-corrected visual acuity (BCVA) of approximately 15 letters in all ranibizumab treatment groups.[4] Other pilot trials had similar results.[5,6] This provided the rationale for 2 large, multicenter trials—Ranibizumab for the Treatment of Macular Edema after *C*entral *R*etinal Vein Occl*UsI*on *S*tudy: *E*valuation of Efficacy and Safety (CRUISE) and the Ranibizuma*B* for the Treatment of Macular Edema after B*RA*nch Retinal *V*ein *O*cclusion: Evaluation of Efficacy and Safety (BRAVO) study—which were designed to determine the efficacy and safety of ranibizumab in patients with macular edema following retinal vein occlusion.[7,8] After 6 monthly intraocular injections of 0.3 mg or 0.5 mg ranibizumab in patients with CRVO, mean improvement in BCVA letter score was 12.7 and 14.9 letters compared with 0.8 letters in the sham injection group. Starting at month 6, all patients were eligible to receive ranibizumab treatment as needed based on prespecified criteria. Herein, we report the 12-month outcomes of CRUISE.

Materials and Methods

Study Design

The CRUISE Study was a 12-month, phase III, multicenter, randomized trial that included a 6-month, injection-controlled treatment period followed by a 6-month observation period, designed to evaluate efficacy and safety of intraocular injections of ranibizumab in patients with macular edema following CRVO. Details of the CRUISE methodology were previously reported[7] and are briefly summarized here. During the treatment period (day 0–month 5) patients received monthly intraocular injections of 0.3 mg or 0.5 mg ranibizumab or sham injections. During the observation period (months 6–11) all patients could receive monthly intraocular ranibizumab if study eye Snellen equivalent BCVA was ≤20/40 or mean central subfield thickness assessed by the investigator was ≥250 μm as measured by Zeiss Stratus 3 (Carl Zeiss Meditec, Inc. Dublin, CA) optical coherence tomography. The CRUISE trial is registered at www.clinicaltrials.gov (NCT00485836; accessed October 20, 2010). The protocol was approved by the institutional review board at each study site, and the study was conducted according to the International Conference on Harmonisation E6 Guideline for Good Clinical Practice and any national requirements. All patients provided informed consent before participation in the study.

Patients

Eligible patients were ≥18 years of age with foveal center-involved macular edema following CRVO diagnosed within 12 months of screening, study eye Snellen equivalent BCVA of 20/40 to 20/320, and mean central subfield thickness ≥250 μm (assessments at both screening and day 0). Patients were randomized 1:1:1 to receive monthly injections of 0.3 mg or 0.5 mg ranibizumab or sham injections for 6 months.[7] Randomization was stratified by study center and baseline BCVA letter score ≤34 (approximate Snellen equivalent <20/200), 35 to 54 (approximate Snellen equivalent 20/200 to <20/80), and ≥55 (approximate Snellen equivalent ≥20/80).

During months 6 through 12, patients continued to be evaluated monthly with a complete eye examination, optical coherence tomography, measurement of vital signs, review of medical history, including concomitant medications and concurrent ocular procedures, and safety assessments. Fluorescein angiography was performed at months 6, 9, and 12. At months 6 and 12, the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) was administered. At each visit from months 6 to 11, all patients with BCVA ≤20/40 or mean central subfield thickness ≥250 μm in the study eye were to receive intraocular ranibizumab. Patients in the 0.3 mg and 0.5 mg groups received their assigned dose; and patients in the sham group, hereafter referred to as the sham/0.5 mg group, received 0.5 mg ranibizumab.

Patients who discontinued the study before the month 12 visit were encouraged to return for an early termination visit 30 days after their last injection and/or study visit to record adverse events (AEs) and serious AEs (SAEs) that had occurred since the patient's last visit and to complete other study assessments.

Outcome Measures

The primary endpoint of CRUISE was mean change from baseline BCVA letter score at month 6. Secondary outcome measures included mean change from baseline BCVA letter score over time to month 12, proportion of patients who gained ≥15 letters from baseline BCVA letter score at month 12, proportion of patients who lost ≥15 letters from baseline BCVA letter score at month 12, mean change from baseline CFT over time to month 12, and proportion of patients with CFT ≤250 μm at month 12. Exploratory and post hoc outcomes included mean change from the baseline NEI VFQ-25 composite score over time to month 12, proportion of patients with study eye Snellen equivalent ≥20/40 at month 12, proportion of patients with study eye Snellen equivalent ≤20/200 at month 12, proportion of patients with >10 retinal hemorrhages over time to month 12, and proportion of patients with zero retinal hemorrhages over time to month 12. Safety outcomes included the incidence and severity of ocular and nonocular AEs and SAEs.

Optical coherence tomography scans, fundus photographs, and fluorescein angiography were evaluated by masked graders at the University of Wisconsin Fundus Photograph Reading Center (Madison, WI); CFT was recorded as the center point thickness provided by Stratus 3 software, unless there was an error in computer recognition of the outer or inner boundaries of the retina or the center point. If the latter occurred, the grader determined CFT with a caliper.

Statistical Analysis

Analyses of efficacy endpoints for the observation period were based on the intent-to-treat population, with subjects grouped according to their assigned treatment. Missing values were imputed using the last-observation-carried-forward method, unless otherwise noted. The study was not powered to compare efficacy outcomes between the treatment groups during the 6-month observation period (i.e., at months 7–12). Thus, efficacy analyses during that time were based on descriptive statistics, and presented statistical comparisons of efficacy outcomes between the sham/0.5 mg and ranibizumab treatment groups were performed post hoc. For visual acuity and CFT outcomes, post hoc subgroup analyses based on month 6 treatment status were performed using observed data (i.e., without imputation for missing values). The incidence of key study eye ocular AEs, SAEs potentially related to VEGF inhibition, and Antiplatelet Trialists' Collaboration[9] arterial throm-

Table 1. Patient Disposition and Treatment

	Sham/0.5 mg (n = 130)	Ranibizumab 0.3 mg (n = 132)	Ranibizumab 0.5 mg (n = 130)
Completed study, n (%)			
Through month 6	115 (88.5)	129 (97.7)	119 (91.5)
Through month 12	109 (83.8)	126 (95.5)	114 (87.7)
Mean number of injections/patient*			
Treatment period	5.4	5.8	5.5
Observation period	3.7	3.8	3.3
Patients receiving first as-needed injection at month 6, n (%)	100 (76.9)	74 (56.1)	64 (49.2)

*During the 6-month treatment period (day 0–month 5), sham patients received sham injections; during the 6-month observation period (months 6–11), sham patients received 0.5 mg ranibizumab if they met prespecified criteria.

boembolic events (ATE) were summarized by treatment group. Safety outcomes for the 0.3 mg and 0.5 mg groups were summarized for the cumulative 12-month study period. Safety outcomes for the sham/0.5 mg group were summarized separately for the treatment and observation periods.

Results

Patient Characteristics and Disposition

We randomized 392 patients to receive intraocular injections of 0.3 mg ranibizumab (n = 132) or 0.5 mg ranibizumab (n = 130) or sham injections (n = 130) at 95 centers in the United States. Patient demographics and baseline ocular characteristics were similar across treatment groups. The mean time from diagnosis of CRVO to screening was 3.3 months (median 2 months for each treatment group), with a duration of ≤3 months in 69% of patients. Mean baseline BCVA letter score was 48.3 letters (approximate Snellen equivalent 20/100) and the mean baseline CFT was 685 μm. Approximately 93% of enrolled patients completed the study through month 6, and 89% completed through month 12 (Table 1). The most common reason for study discontinuation was physician's decision. During the 6-month observation period, the percentage of patients treated with ranibizumab when the protocol-specified treatment criteria were met ranged from 79% to 94% across treatment groups and time points. Between months 6 and 12, the mean number of as-needed ranibizumab injections among all randomized patients was 3.8, 3.3, and 3.7 in the 0.3 mg, 0.5 mg, and sham/0.5 mg groups; and the percentage of patients who did not receive any injections during the observation period was 9.1%, 14.6%, and 15.4%, respectively. Twenty-nine of the 392 patients discontinued from the study before month 6. Excluding those patients, the mean number of as-needed ranibizumab injections received during the observation period was 3.9, 3.6, and 4.2 in the 0.3 mg, 0.5 mg, and sham/0.5 mg groups; and the percentage of patients who did not receive any injections during the observation period was 7.0, 6.7, and 4.3, respectively.

Functional Outcomes at Month 12

Change from Baseline BCVA. At month 6, the primary endpoint, the mean change from baseline BCVA letter score was 12.7 and 14.9 in the 0.3 mg and 0.5 mg ranibizumab groups compared with 0.8 in the sham group. In the 0.3 mg and 0.5 mg treatment groups, these improvements were maintained with as-needed ranibizumab during the observation period, with a mean (95% confidence interval) change from baseline BCVA letter score of 13.9 (11.2–16.5) and 13.9 (11.5–16.4), respectively, at month 12.

The sham/0.5 mg group experienced an overall improvement in BCVA letter score during the observation period, with a mean (95% confidence interval) change from baseline of 7.3 (4.5–10.0) at month 12. The mean improvement from baseline BCVA at month 12 in the sham/0.5 mg group was significantly less than that of the 0.3 mg and 0.5 mg treatment groups ($P<0.001$ for each ranibizumab group vs sham/0.5 mg; Fig 1).

From months 6 to 7, the mean BCVA letter score decreased in the 0.3 mg and 0.5 mg groups and increased in the sham/0.5 mg group. Across treatment groups, 43.9% (0.3 mg), 50.8% (0.5 mg), and 23.1% (sham/0.5 mg) of patients did not receive ranibizumab treatment at month 6. Most patients who did not receive an injection showed worsening of BCVA from month 6 to 7, with mean decreases in BCVA letter score of 4.6 (0.3 mg), 7.2 (0.5 mg), and 2.4 (sham/0.5 mg), whereas most of those who received an injection showed improvement in BCVA, with mean increases of 1.7 (0.3 mg and 0.5 mg) and 4.9 (sham/0.5 mg; Fig 2, available online at http://aaojournal.org).

Percentage of Patients Who Had a BCVA Letter Score Gain or Loss ≥15. The percentage of patients who had an improvement from baseline BCVA letter score of ≥15 at the month 6 time point was 46.2% (0.3 mg) and 47.7% (0.5 mg) in the ranibizumab groups and 16.9% in the sham group. This was maintained in the ranibizumab groups during the observation period when ranibizumab was given as needed, and at month 12 the percentage of patients who had an improvement from baseline BCVA letter score ≥15 was 47.0% (0.3 mg) and 50.8% (0.5 mg; Table 2). The sham/0.5 mg group showed improvement from ranibizumab injections given as needed throughout the observation period; however, the 33.1% of patients who gained ≥15 in BCVA letter score at month 12 was less than that observed in the ranibizumab groups ($P<0.05$ for each ranibizumab group vs sham/0.5 mg). The percentage of patients who lost ≥15 from baseline BCVA letter score was 3.8% (0.3 mg), 1.5% (0.5 mg), and 15.4% (sham) at month 6 compared with 3.8% (0.3 mg), 2.3% (0.5 mg), and 10.0% (sham/0.5 mg) at month 12.

Percentage of Patients with Snellen Equivalent BCVA ≥20/40. A Snellen BCVA of ≥20/40 is generally sufficient to support reading and driving and is considered an excellent outcome. The percentage of patients with Snellen equivalent BCVA ≥20/40 was 43.9% (0.3 mg), 46.9% (0.5 mg), and 20.8% (sham) at month 6, compared with 43.2% (0.3 mg), 43.1% (0.5 mg), and 34.6% (sham/0.5 mg) at month 12. Snellen equivalent BCVA outcomes are broken down into several categories in Table 3.

Percentage of Patients with Snellen Equivalent BCVA ≤20/200. Snellen equivalent BCVA ≤20/200 is a poor visual outcome and is defined as legal blindness. This outcome occurred in the study eye in 15.2% (0.3 mg), 11.5% (0.5 mg), and 27.7% (sham) of patients at month 6, compared with 12.1% (0.3 mg), 12.3% (0.5 mg), and 20.0% (sham/0.5 mg) at month 12.

Impact of Visual Outcome on Daily Life Activities. At month 6, the mean increase from baseline NEI VFQ-25 composite score was 7.1 points (0.3 mg) and 6.2 points (0.5 mg) in the ranibizumab-treatment groups compared with 2.8 points in the sham group. Treatment with ranibizumab as needed from months 6–11 maintained, on average, the increases in the 2 ranibizumab groups (7.1 points in the 0.3 mg group and 6.6 points in the 0.5 mg group) and resulted in an increase (from baseline) of 5.0 points in the sham/0.5 mg group (Fig 3).

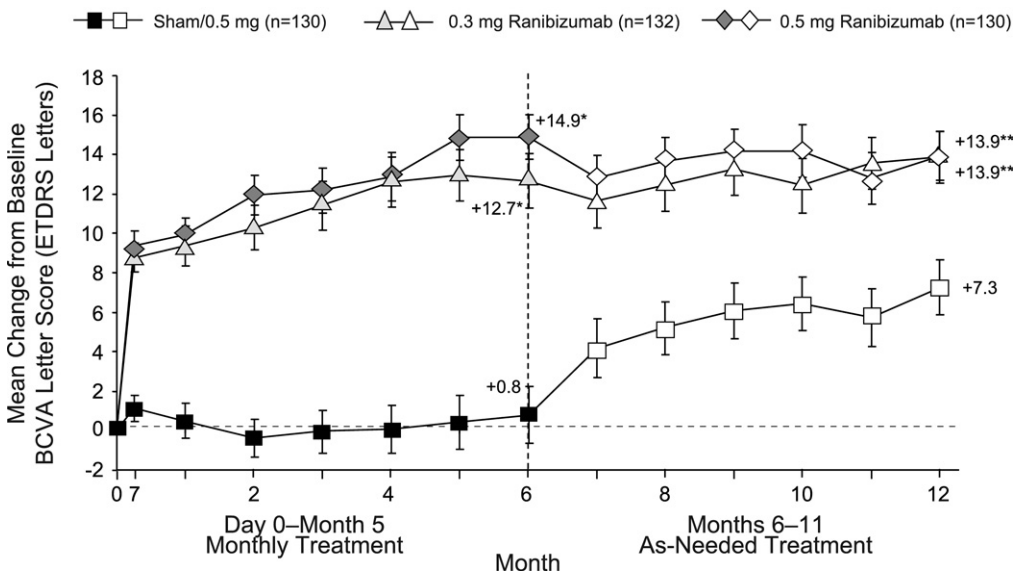

Figure 1. Mean change from study eye baseline best-corrected visual acuity letter score over time to month 12. *$P<0.0001$ versus sham, **$P<0.001$ versus sham/0.5 mg. Earliest statistically significant group difference was at day 7. The last-observation-carried-forward method was used to impute missing values. Vertical bars are ±1 standard error of the mean. On average, visual gains during the treatment period were maintained in the ranibizumab treatment groups during the observation period. There was substantial improvement in visual acuity in the sham/0.5 mg group during the observation period; however, the mean change from baseline best-corrected visual acuity score of the sham/0.5 mg patients remained significantly different from that of the 0.3 mg and 0.5 mg groups at month 12. BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study.

Table 2. Change from Baseline Study Eye Best-Corrected Visual Acuity at Month 12

	Sham/0.5 mg (n = 130)	Ranibizumab 0.3 mg (n = 132)	Ranibizumab 0.5 mg (n = 130)
Change from baseline BCVA (ETDRS letter score) at month 12			
Mean (SD)	7.3 (15.9)	13.9 (15.2)	13.9 (14.2)
95% CI for mean	4.5-10.0	11.2-16.5	11.5-16.4
Difference in means (vs. sham/0.5 mg)		6.6	6.7
95% CI for difference		2.8-10.4	3.0-10.4
P-value (ranibizumab vs. sham/0.5 mg)		0.0007	0.0006
Distribution of change at month 12, n (%)			
Gain (letters)			
≥15	43 (33.1)	62 (47.0)	66 (50.8)
10–14	22 (16.9)	23 (17.4)	20 (15.4)
5–9	13 (10.0)	21 (15.9)	14 (10.8)
No change, ±4.0	29 (22.3)	13 (9.8)	23 (17.7)
Loss (letters)			
5–9	7 (5.4)	6 (4.5)	2 (1.5)
10–14	3 (2.3)	2 (1.5)	2 (1.5)
≥15	13 (10.0)	5 (3.8)	3 (2.3)
≥15-letter gain, %			
Month 7	25.4	42.4	43.1
Month 8	26.2	43.9	53.8
Month 9	31.5	43.2	48.5
Month 10	31.5	45.5	51.5
Month 11	30.8	45.5	46.2

BCVA = best-corrected visual acuity; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation. Last-observation-carried forward method was used to impute missing data.

Anatomic Outcomes at Month 12

Change from Baseline CFT. At the month 6 time point, the mean change from baseline CFT was a reduction of 433.7 and 452.3 μm in the 0.3 mg and 0.5 mg ranibizumab groups compared with a reduction of 167.7 μm in the sham group. In the 0.3 mg and 0.5 mg treatment groups, these reductions were maintained with as-needed ranibizumab during the observation period, with a mean reduction from baseline CFT of 452.8 and 462.1 μm, respectively, at month 12 (Fig 4). The sham/0.5 mg group experienced an overall improvement in CFT during the observation period, with a mean reduction from baseline of 427.2 μm at month 12. The mean improvement from baseline CFT at month 12 in the sham/0.5 mg group was not significantly less than that of the 0.3 mg or 0.5 mg treatment groups ($P>0.40$ for each ranibizumab group vs sham/0.5 mg).

Most patients in the 0.3 mg, 0.5 mg, and sham/0.5 mg groups who did not receive an injection of as-needed ranibizumab at month 6 showed worsening of CFT from months 6 to 7, with mean increases of 176, 200, and 21 μm, respectively, from months 6 to 7, whereas most who received an injection showed improvement or no change in CFT from months 6 to 7, with mean reductions of 11, 19, and 295 μm, respectively, from months 6 to 7 (Fig 5, available online at http://aaojournal.org).

Residual Edema. In addition to assessing the absolute reduction in CFT, it is important to determine how much macular edema a treatment eliminates. One way to assess this is to determine the percentage of patients with CFT ≤250 μm. At the month 6 time point, 75.0% (0.3 mg) and 76.9% (0.5 mg) of ranibizumab-treated patients had CFT ≤250 μm compared with 23.1% of the sham group patients. At month 12, the percentages in the ranibizumab groups were similar to those at month 6—75.8% (0.3 mg) and 77.7% (0.5 mg)—and had increased markedly to 70.8% in the sham/0.5 mg group (Table 4).

Retinal Hemorrhages. Indirect ophthalmoscopy and/or biomicroscopy by investigators indicated that 0.8% (0.3 mg), 1.5 % (0.5

Table 3. Snellen Equivalent Study Eye Best-Corrected Visual Acuity (BCVA)

Study Eye BCVA (Approximate Snellen Equivalent), n (%)	Baseline			Month 6*			Month 12*		
		Ranibizumab			Ranibizumab			Ranibizumab	
	Sham (*n* = 130)	*0.3 mg* (*n* = 132)	*0.5 mg* (*n* = 130)	*Sham*† (*n* = 130)	*0.3 mg* (*n* = 132)	*0.5 mg* (*n* = 130)	*Sham/0.5 mg*† (*n* = 130)	*0.3 mg* (*n* = 132)	*0.5 mg* (*n* = 130)
≥20/20	0	0	0	2 (1.5)	8 (6.1)	17 (13.1)	9 (6.9)	9 (6.8)	11 (8.5)
20/25–20/40	12 (9.2)	9 (6.8)	7 (5.4)	25 (19.2)	50 (37.9)	44 (33.8)	36 (27.7)	48 (36.4)	45 (34.6)
20/50–20/63	36 (27.7)	28 (21.2)	38 (29.2)	26 (20.0)	17 (12.9)	21 (16.2)	23 (17.7)	27 (20.5)	30 (23.1)
20/80–20/160	47 (36.2)	54 (40.9)	46 (35.4)	41 (31.5)	37 (28.0)	33 (25.4)	36 (27.7)	32 (24.2)	28 (21.5)
20/200–20/500	35 (26.9)	40 (30.3)	39 (30.0)	31 (23.8)	18 (13.6)	15 (11.5)	25 (19.2)	16 (12.1)	15 (11.5)
<20/500	0	1 (0.8)	0	5 (3.8)	2 (1.5)	0	1 (0.8)	0	1 (0.8)

Baseline and month 6 data are based on month 6 database.
*Last-observation-carried forward method was used to impute missing data.
†During the 6-month treatment period (day 0–month 5), sham patients received sham injections; during the 6-month observation period (month 6–11), sham patients received 0.5 mg ranibizumab if they met prespecified criteria.

mg), and 1.5% (sham) of patients had no intraretinal hemorrhages at baseline (Fig 6, available online at http://aaojournal.org), whereas 82.6%, 87.7%, and 86.9%, respectively, had >10 hemorrhages. A greater increase was observed in the percentage of patients with no intraretinal hemorrhage in the 0.3 mg and 0.5 mg groups compared with the sham group at month 6 and the sham/0.5 mg group at month 12; and the percentage of patients who had >10 intraretinal hemorrhages decreased more rapidly in the ranibizumab treatment groups compared with the sham/0.5 mg group.

Safety Outcomes at Month 12

Key study eye AEs were infrequent, and the only one with a greater incidence in the ranibizumab groups during the 12-month study period compared with the sham group during the first 6 months and the sham/0.5 mg group during the second 6 months was cataract (Table 5). If this small increase in the incidence of cataract in the ranibizumab groups—3.8% (0.3 mg; 12-month rate) and 7.0% (0.5 mg; 12-month rate) compared with 0% (sham; 6-month rate)—was not due to chance, it could have been related to the procedure (intraocular injections) or to ranibizumab.

There were few nonocular SAEs potentially related to VEGF inhibition (Table 6). Throughout the 12-month study, there were 2 such SAEs in the 0.3-mg group and 4 in the 0.5 mg group, compared with 2 SAEs in the sham group during the first 6 months. This included 1 Antiplatelet Trialists' Collaboration ATE in the 0.3-mg group, 3 in the 0.5 mg group, and 1 in the sham group. There were no nonocular SAEs potentially related to VEGF inhibition in the sham/0.5 mg group between months 6 and 12, when patients were received ranibizumab injections as needed.

Discussion

Monthly intraocular injections of 0.3 mg or 0.5 mg of ranibizumab for 6 months provided substantial benefit in

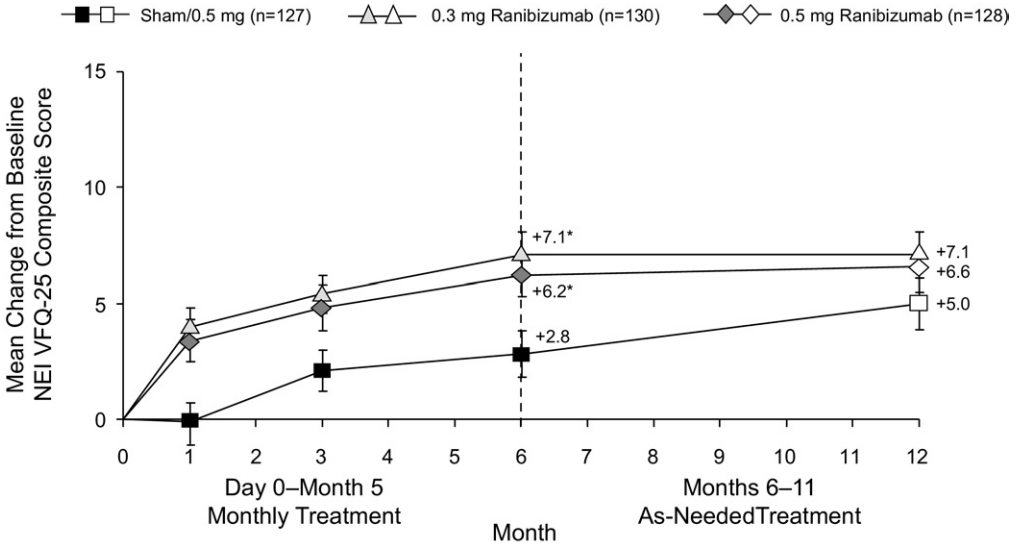

Figure 3. Mean change from baseline National Eye Institute Visual Function Questionnaire-25 composite score over time to month 12. *$P<0.01$ versus sham. The last-observation-carried-forward method was used to impute missing data. Vertical bars are ±1 standard error of the mean. The composite score increased rapidly and was significantly greater in the ranibizumab treatment groups compared with the sham group at month 6. During the observation period, on average, the composite score remained stable in the ranibizumab groups and increased substantially in the sham/0.5 mg group, which was no longer significantly different than the ranibizumab groups at month 12. NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25.

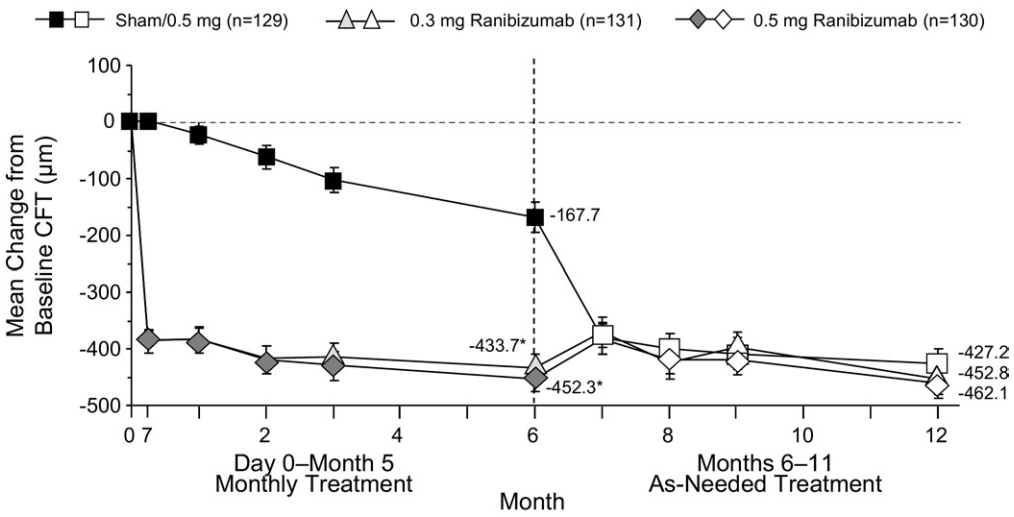

Figure 4. Mean change from baseline central foveal thickness over time to month 12. Month 6 values are based on month 6 database. *$P<0.0001$ versus sham. The last-observation-carried-forward method was used to impute missing values. The earliest significant group difference was at day 7. Vertical bars are ±1 standard error of the mean. On average, improvements in central foveal thickness during the treatment period were maintained in the ranibizumab groups during the observation period. There was substantial improvement in the sham/0.5 mg group during the observation period, and the mean change from baseline central foveal thickness of sham/0.5 mg patients was similar to that of the 0.3 mg and 0.5 mg groups at month 12. CFT = central foveal thickness.

patients with CRVO, resulting in mean improvements from baseline BCVA letter score of 12.7 and 14.9. This benefit was maintained during the subsequent 6 months in which injections were given only if retreatment criteria were met, so that at 12 months, the mean improvement in BCVA letter score was 13.9 in each ranibizumab treatment group. This indicates that after a period of aggressive treatment with ranibizumab, visual benefits can be maintained by close follow-up and treatment if there is evidence of persistent or recurrent disease. What is not answered by this trial is whether even better visual outcomes would have resulted by continuing monthly injections during the second 6 months of the study. In fact, the trial was designed to ensure that during the observation period, patients who might benefit from ranibizumab treatment would receive it. It was thought that even if CFT was ≤250 μm, patients should continue to receive treatment, unless their BCVA had improved to the point that one could potentially question whether the risk/benefit ratio favored another injection. It was our judgment that this level was ≥20/40. However, some investigators questioned whether a patient with CFT ≤250 μm should receive an injection, regardless of BCVA, and deferred treatment. This could be a source of undertreatment during the observation period. It is clear that although monthly injections of ranibizumab suppressed the effects of VEGF in the majority of patients, they did not eliminate VEGF production, because the majority of patients who did not receive an injection of ranibizumab at month 6 had an increase in CFT and reduced vision and required an injection at month 7. During the observation period, recurrent/persistent edema or BCVA ≤20/40 was common, necessitating an injection of ranibizumab approximately two thirds of the time in each of the groups.

Table 4. Study Eye Central Foveal Thickness

	Sham/0.5 mg (n = 130)	Ranibizumab	
		0.3 mg (n = 132)	*0.5 mg (n = 130)*
Baseline, n (%)			
≤250 μm	2 (1.6)	4 (3.1)	6 (4.6)
>250–400 μm	14 (10.9)	8 (6.1)	8 (6.2)
>400 μm	113 (87.6)	119 (90.8)	116 (89.2)
Month 6*, n (%)			
≤250 μm	30 (23.1)	99 (75.0)	100 (76.9)
>250–400 μm	17 (13.1)	14 (10.6)	12 (9.2)
>400 μm	83 (63.8)	19 (14.4)	18 (13.8)
Month 12*, n (%)			
≤250 μm	92 (70.8)	100 (75.8)	101 (77.7)
>250–400 μm	14 (10.8)	11 (8.3)	13 (10.0)
>400 μm	24 (18.5)	21 (15.9)	16 (12.3)

Baseline and month 6 data are based on month 6 database. One sham/0.5 mg patient and one 0.3 mg patient did not have an assessment at baseline.
*Last-observation-carried-forward method was used to impute missing data at post baseline time points.

On average, there was substantial improvement in the sham/0.5 mg group during the observation period when patients received injections of 0.5 mg of ranibizumab if they met retreatment criteria. In fact, after 77% of sham/0.5 mg patients received an injection of 0.5 mg ranibizumab at month 6, there was a dramatic reduction in macular edema at month 7, and mean CFT was similar to that in the 2 ranibizumab treatment groups and remained so through month 12. There was also substantial improvement in BCVA in the sham/0.5 mg group during the observation period; however, unlike the mean CFT, which no longer differed from that of the 0.3 mg and 0.5 mg ranibizumab groups at month 7 and beyond, there remained a significant difference in mean improvement from baseline BCVA at month 12 between the sham/0.5 mg group and the 0.3 mg

Table 5. Key Study Eye Adverse Events through Month 12[†]

Adverse Events, n (%)	Sham* Day 0–Month 6 (n = 129)	Sham/0.5 mg[†] Months 6–12 (n = 110)	Ranibizumab 0.3 mg Day 0–Month 12 (n = 132)	Ranibizumab 0.5 mg Day 0–Month 12 (n = 129)
Any intraocular inflammation event (iridocyclitis, iritis, vitritis)	5 (3.9)	2 (1.8)	3 (2.3)	2 (1.6)
Endophthalmitis	0	0	0	0
Lens damage	0	0	0	0
Cataract	0	2 (1.8)[‡]	5 (3.8)	9 (7.0)
Iris neovascularization	9 (7.0)	2 (1.8)	2 (1.5)	5 (3.9)
Neovascular glaucoma	2 (1.6)	0	0	1 (0.8)
Rhegmatogenous retinal detachment	0	0	0	0
Retinal tear	0	2 (1.8)[‡]	0	2 (1.6)
Vitreous hemorrhage	9 (7.0)[‡]	2 (1.8)[‡]	7 (5.3)	7 (5.4)

*Outcomes during 6-month treatment period for safety-evaluable sham-group patients (received ≥1 sham injection).
[†]Outcomes during 6-month observation period for safety-evaluable sham/0.5 mg group patients (i.e., received at least one 0.5 mg ranibizumab injection).
[‡]One event reported as serious.

and 0.5 mg groups. Just as it is unknown whether the 0.3 mg and 0.5 mg groups may have had even better outcomes at month 12 if they had continued to receive monthly injections of ranibizumab during the second 6 months of the study, it is unknown whether the sham/0.5 mg group would have had even greater improvement if monthly injections were mandated; however, what is clear is that a 6-month period of monthly treatments followed by treatment as needed for 6 months is superior to observation for 6 months followed by treatment as needed for 6 months. This suggests that there may be a visual penalty incurred by delaying ranibizumab injections in patients with macular edema following CRVO.

In addition to providing a major impact on macular edema, monthly injections of ranibizumab accelerated the resolution of retinal hemorrhages. The mechanism by which hemorrhages are cleared from the retina is not completely understood, but it is felt that macrophages and microglia

Table 6. Key Nonocular Serious Adverse Events through Month 12

	Sham* Day 0–Month 6 (n = 129)	Sham/0.5 mg[†] Months 6–12 (n = 110)	Ranibizumab 0.3 mg Day 0–Month 12 (n = 132)	Ranibizumab 0.5 mg Day 0–Month 12 (n = 129)
Serious Adverse Events Potentially Related to VEGF Inhibition, n (%)				
Hemorrhagic stroke	0	0	0	0
Ischemic stroke	0	0	0	1 (0.8)
Transient ischemic attack	0	0	1 (0.8)	1 (0.8)[‡]
Myocardial infarction	1 (0.8)	0	1 (0.8)	1 (0.8)
Angina pectoris	0	0	0	1 (0.8)[‡]
Hypertension	1 (0.8)	0	0	0
Nonocular hemorrhage, other	0	0	0	0
Proteinuria	0	0	0	0
APTC ATEs, n (%)	1 (0.8)	0	1 (0.8)	3 (2.3)
Vascular death	0	0	0	0
Death from unknown cause	0	0	0	1 (0.8)
Nonfatal myocardial infarction	1 (0.8)	0	1 (0.8)	1 (0.8)
Nonfatal hemorrhagic stroke	0	0	0	0
Nonfatal ischemic stroke	0	0	0	1 (0.8)

APTC ATEs = Antiplatelet Trialists' Collaboration arterial thromboembolic events; VEGF = vascular endothelial growth factor.
*Outcomes during 6-month treatment period for safety-evaluable sham-group patients (i.e., received at least one sham injection).
[†]Outcomes during 6-month observation period for safety-evaluable sham/0.5 mg group patients (i.e., received at least one 0.5 mg ranibizumab injection).
[‡]Both events occurred in the same patient.

play a role. Because VEGF promotes influx of macrophages in the retina, and this is suppressed by VEGF blockade, it is unlikely that ranibizumab accelerates the removal of hemorrhages from the retina. Another possibility is that hemorrhages do not occur all at once at the onset of retinal vein occlusion, but rather are ongoing. Perhaps the large and sustained increases in VEGF that occur in retinal vein occlusions compromise the blood–retinal barrier to such an extent that influx of red blood cells accompanies influx of plasma. Thus, the rate of clearance of hemorrhage may result from 2 opposing processes: Ongoing hemorrhage that is gradually reduced under normal circumstances, and removal of hemorrhages by macrophages and microglia. Ranibizumab may help to reduce the influx of RBCs, just as it reduces influx of plasma, and thus tip the balance toward hemorrhage removal, resulting in more rapid clearance of hemorrhages.

These data suggest that RVOs are not simply acute events followed by gradual recovery that is accelerated by blockade of VEGF. Instead, it seems that vascular occlusion is an inciting event that causes reduced perfusion, retinal ischemia, and increased production of VEGF. The level of upregulation of VEGF is likely to be influenced by several factors, including the amount of compromise of perfusion from the occlusion itself (possibly related to the location or extent of occlusion); the amount of preexistent arterial insufficiency; and the amount of retinal infarction, which can reduce the total area of retinal ischemia. If the upregulation of VEGF is sufficiently high, it can become a major exacerbating factor. This may explain why the level of VEGF at baseline has an inverse correlation with visual outcome.[4]

In conclusion, 6 monthly intraocular injections of ranibizumab in patients with CRVO resulted in large gains in BCVA and improved quality of life that were maintained over a subsequent 6 months during which ranibizumab was given as needed. Patients met retreatment criteria and received injections roughly two thirds of the time during the observation period, and it is likely that treatment for longer than a year will be needed for many patients, as demonstrated in a previous uncontrolled trial.[10] Additional studies are needed to provide longer follow-up of patients with CRVO treated with ranibizumab to determine whether dependence on injections is reduced over time and whether strategies such as scatter photocoagulation to areas of retinal nonperfusion provide added benefit.

Acknowledgments. The authors thank Roberta Kelly of Genentech, Inc., for editing, formatting, and preparation of figures.

References

1. Klein R, Moss SE, Meuer SM, Klein BE. The 15-year cumulative incidence of retinal vein occlusion: the Beaver Dam Eye Study. Arch Ophthalmol 2008;126:513–8.
2. Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in Australia: the Blue Mountains Eye Study. Arch Ophthalmol 1996;114:1243–7.
3. Green WR, Chan CC, Hutchins GM, Terry JM. Central vein occlusion: a prospective histological study of 29 eyes in 28 cases. Trans Am Ophthalmol Soc 1981;79:371–422.
4. Campochiaro PA, Hafiz G, Shah SM, et al. Ranibizumab for macular edema due to retinal vein occlusions: implication of VEGF as a critical stimulator. Mol Ther 2008;16:791–9.
5. Spaide RF, Chang LK, Klancnik JM, et al. Prospective study of intravitreal ranibizumab as a treatment for decreased visual acuity secondary to central retinal vein occlusion. Am J Ophthalmol 2009;147:298–306.
6. Pieramici DJ, Rabena M, Castellarin AA, et al. Ranibizumab for the treatment of macular edema associated with perfused central retinal vein occlusions [report online]. Ophthalmology 2008;115:e47–54. Available at: http://www.ophthalmologyjournaloftheaao.com/article/S0161-6420%2808%2900634-9/abstract. Accessed February 21, 2011.
7. Brown DM, Campochiaro PA, Singh RP, et al, CRUISE Investigators. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology 2010;117:1124–33.
8. Campochiaro PA, Heier JS, Feiner L, et al, BRAVO Investigators. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary endpoint results of a phase III study. Ophthalmology 2010;117:1102–12.
9. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81–106.
10. Campochiaro PA, Hafiz G, Channa R, et al. Antagonism of vascular endothelial growth factor for macular edema caused by retinal vein occlusion: two-year outcomes. Ophthalmology 2010;117:2387–94.

Footnotes and Financial Disclosures

Originally received: December 21, 2010.
Final revision: February 19, 2011.
Accepted: February 21, 2011.
Available online: June 29, 2011. Manuscript no. 2010-1755.

[1] Departments of Ophthalmology and Neuroscience, The Johns Hopkins School of Medicine, Baltimore, Maryland.

[2] Retinal Consultants of Houston, Houston, Texas.

[3] Tennessee Retina, Nashville, Tennessee.

[4] Retina Research Institute of Texas, Abilene, Texas.

[5] Genentech, Inc., South San Francisco, California.

Presented in part at: the American Association for Research in Vision and Ophthalmology (ARVO), May 2–6, 2010, Fort Lauderdale, Florida; World Ophthalmology Congress (WOC), June 5–9, 2010, Berlin, Germany; American Society of Retina Specialists (ASRS), August 28–September 1, 2010, Vancouver, British Columbia; Retina Society, September 23–26, 2010, San Francisco, California; American Academy of Ophthalmology (AAO), October 16–19, 2010, Chicago, Illinois.

Financial Disclosure(s):
Financial disclosure/conflict of interest: Genentech, Inc., South San Francisco, California, provided support for the study and participated in study design, conducting the study, and data collection, management, and interpretation.

Peter A. Campochiaro – Alcon – Financial Support; Alimera – Financial Support; Genentech – Financial Support, Consultant; Bristol-Myers Squibb (past) – Consultant; Genzyme – Financial Support; LPath – Consultant; Regeneron – Consultant; Molecular Partners – Financial Support; GlaxoSmithKline – Financial Support, Consultant; Oxford Biomedical – Financial Support; Pfizer – Consultant.

David M. Brown – Alcon – Consultant, Financial Support; Alimera – Consultant, Financial Support; Allergan – Consultant, Financial Support; Eli Lilly – Financial Support; Genentech – Consultant, Lecturer, Financial Support; Heidelberg – Consultant, Financial Support; Molecular Partners – Consultant, Financial Support; Novartis – Consultant, Lecturer, Financial Support; Paloma – Consultant, Financial Support; Regeneron – Consultant, Financial Support; Schering Plough – Financial Support; Thrombogenics – Financial Support; Steba Biotech – Consultant, Financial Support; Zeiss – Consultant, Financial Support.

Carl C. Awh – Arctic DX – Consultant, Equity Ownership/Stock Options; Bausch and Lomb – Consultant, Lecturer; Genentech – Consultant, Lecturer; Notal, Consultant; Synergetics; DX – Consultant, Equity Ownership/Stock Options, Patents/Royalties; Volk Optical, Consultant.

Sarah Gray – Genentech – Employee; Roche – Equity Ownership/Stock Options.

Namrata Saroj – Genentech – Employee; Roche – Equity Ownership/Stock Options.

Anthony P. Adamis – Genentech – Employee; Roche – Equity Ownership/Stock Options.

Wendy Yee Murahasi – Genentech – Employee; Roche – Equity Ownership/Stock Options.

Roman G. Rubio – Genentech – Employee; Roche – Equity Ownership/Stock Options.

Correspondence:

Peter A. Campochiaro, MD, 719 Maumenee, The Wilmer Eye Institute, The Johns Hopkins School of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287-9277. E-mail: pcampo@jhmi.edu