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Long-term Outcomes in Ranibizumab-Treated Patients With Retinal Vein Occlusion; The Role of Progression of Retinal Nonperfusion

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Abstract

PURPOSE—To determine the percentage of ranibizumab-treated patients with retinal vein occlusion (RVO) who had resolution of edema for at least 6 months after the last injection, along with factors and outcomes that correlate with resolution.

DESIGN—Post hoc analysis of open-label clinical trial.

METHODS—Twenty patients with branch RVO (BRVO) and 20 with central RVO (CRVO) received ranibizumab monthly for 3 months and as needed for recurrent/persistent macular edema, no more frequently than every 2 months. Patients still requiring injections after month 40 received scatter and grid laser photocoagulation to try to reduce the need for injections. Main outcome measures included the percentage of patients who had resolution of edema, change in best-corrected visual acuity (BCVA) from baseline, and change in area of retinal nonperfusion in central subfields.

RESULTS—Nine patients with BRVO (45%) had edema resolution from injections alone after a mean of 20.2 months, 4 resolved after addition of laser, 4 were unresolved through 72 months, and 3 exited prior to resolution. Five patients with CRVO (25%) resolved from injections alone after a mean of 14.0 months, 8 remained unresolved through 72 months despite addition of laser, and 7 exited prior to resolution. For BRVO or CRVO, there was a negative correlation between posterior retinal nonperfusion area and BCVA at months 18, 24, and 36 ($P < .05$).

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CONCLUSIONS—In patients with RVO, infrequent ranibizumab injections to control edema may not be sufficient to prevent progression of retinal nonperfusion, which may contribute to loss of visual gains.

Retinal vein occlusion (RVO) consists of central RVO (CRVO) and branch RVO (BRVO), which are prevalent retinal vascular diseases. In patients with CRVO, thrombosis of the main outflow vessel of the retina results in variable amounts of hemorrhage, edema, and retinal nonperfusion throughout the retina, whereas in patients with BRVO there is occlusion of a proximal branch of the central retinal vein that results in similar findings throughout about half of the retina. Hemorrhages and edema were assumed to be attributable to elevated intraluminal pressure, but the development of ranibizumab (Lucentis; Genentech, Inc, South San Francisco, California, USA), a Fab fragment that specifically binds all isoforms of vascular endothelial growth factor A (VEGF), made it possible to test the hypothesis that VEGF contributes to the edema, and the hypothesis was found to be correct.¹ This has been confirmed by the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO)² and Treatment of Macular Edema following Central Retinal Vein Occlusion: Evaluation of Efficacy and Safety (CRUISE)³ trials. In BRAVO, monthly injections of 0.3 or 0.5 mg ranibizumab for 6 months resulted in gains in mean letter score from baseline BCVA of 16.6 and 18.3, compared to 7.3 in the sham injection group.² In CRUISE, at the month 6 primary endpoint, there was a mean improvement from baseline in BCVA letter score of 12.7 (0.3 mg) and 14.9 (0.5 mg) vs 0.8 (sham).³ These gains were maintained between months 6 and 12 by intermittent injections of ranibizumab for recurrent/persistent edema.^{4,5} Thus, in patients with RVO, blockade of VEGF with ranibizumab reduces edema and improves vision. Monthly injections of ranibizumab also resulted in more rapid resolution of retinal hemorrhages than sham injections, indicating that high levels of VEGF contribute to retinal hemorrhages as well as macular edema.^{4,5}

These outcomes are outstanding, and it was hoped that they would be maintained and the need for injections would be eliminated as collaterals developed and circumvented the obstruction. However, 2-year follow-up of patients entered in the original ranibizumab study¹ showed that many patients with BRVO or CRVO still required injections for chronic, recurrent macular edema and that injection only as frequently as every 2 months allowed maintenance of early visual gains in patients with BRVO, but was associated with some reduction in visual gains in patients with CRVO.⁶ Findings were similar in the much larger HORIZON trial, in which after 12 months of treatment with ranibizumab in BRAVO and CRUISE, patients with RVO were seen at least every 3 months and given an injection of ranibizumab for recurrent/persistent macular edema.⁷ These data suggest that many patients with RVO still require frequent anti-VEGF injections 24 months after the onset of treatment and that long-term outcomes are unknown. We now report long-term outcomes for patients with RVO enrolled in the original ranibizumab study.¹

SUBJECTS AND METHODS

The focus of this report is long-term follow-up of a study^{1,6} that was approved by the institutional review board (IRB) of Johns Hopkins University School of Medicine. The study

was registered on December 1, 2006 at www.clinicaltrials.gov (NCT00407355) and conducted in compliance with the Declaration of Helsinki, US Code 21 of Federal Regulations, and the Harmonized Tripartite Guidelines for Good Clinical Practice (1996). All patients provided informed consent before participation in the study. Twenty patients with BRVO and 20 patients with CRVO were randomized 1:1 to receive either 0.3 mg or 0.5 mg ranibizumab monthly for 3 months. Patients were seen at months 4, 5, 6, 9, and 12, and an attempt was made to hold injections to determine whether a period of rebound edema would be followed by final resolution of edema, but if edema persisted for several months and there was concern that it was a threat to the patient's long-term visual potential, an injection of 1.25 mg bevacizumab was allowed. Beginning at month 12, patients were seen every 2 months and given an injection of ranibizumab if time-domain optical coherence tomography (OCT) demonstrated recurrent edema involving the fovea. Three patients with CRVO reached the month 12 visit before the approval of the amendment allowing for ranibizumab injections and received an injection of bevacizumab at month 12. Beginning at month 40, in addition to being eligible for as-needed treatment with ranibizumab, patients with evidence of recurrent macular edema by OCT underwent ultra-widefield fluorescein angiography and received scatter laser photocoagulation to all areas of retinal nonperfusion outside the fovea, followed by an injection of ranibizumab. If edema persisted and required 2 consecutive injections after laser treatment, ultra-widefield fluorescein angiography was repeated and supplemental scatter laser photocoagulation was done along with grid laser to areas of leakage in the macula but outside the foveal avascular zone. This was also followed by an injection of ranibizumab.

At each study visit the patient had best-corrected visual acuity (BCVA) measured by an experienced examiner using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol,⁸ OCT performed by an experienced investigator with a Stratus OCT3 (Carl Zeiss Meditec, Dublin, California, USA) using the Fast Macular Scan protocol, and a complete eye examination. Serial 7-field fluorescein angiography (FA) and color fundus photographs using a 30-degree lens were performed at baseline and at months 1, 3, 4, 18, 24, 30, and 36. Ultra-widefield FAs using the Optos P200Tx (Optos, Dunfermline, Scotland) were performed at the first study visit after month 36, on each visit in which laser treatment was given, and at months 48 and 60.

ADMINISTRATION OF STUDY DRUG

Povidone-iodine was used to clean the lids and a lid speculum was inserted. Topical anesthesia was applied and the conjunctiva was irrigated with 5% povidone-iodine. A 30-gauge needle was inserted through the pars plana and 0.05 mL ranibizumab was injected into the vitreous cavity. Funduscopy examination was done to confirm retinal perfusion.

LASER PHOTOCOAGULATION

Areas of retinal nonperfusion were treated with 200- to 500- μ m burns 1 burn width apart. It was also assumed that there was additional nonvisualized retinal nonperfusion in the far periphery and 5 rows of laser photocoagulation were given for 360 degrees for patients with CRVO and roughly 180–200 degrees for patients with BRVO (the 2 quadrants affected by the BRVO) starting just posterior to the aura serrata. An injection of ranibizumab was given

after completion of the laser photocoagulation and the patient was seen every 2 months and treated with ranibizumab if there was recurrent/persistent macular edema. If a ranibizumab injection was required on 2 consecutive visits after laser, supplemental laser photocoagulation was given to provide complete scatter photocoagulation of the peripheral retina to within 2 disc diameters of the arcade vessels and grid laser photocoagulation (100- μ m burns 1 burn width apart) was given to areas of diffuse leakage in the macula but outside the foveal avascular zone. An injection of ranibizumab was given after the laser. If injections of ranibizumab were needed on 2 consecutive visits after the second laser treatment, remaining retina outside the arcade vessels was treated, followed by an injection of ranibizumab. Patients were then seen every 2 months and treated with ranibizumab for recurrent edema.

MEASUREMENT OF AREA OF POSTERIOR RETINAL NONPERFUSION

Areas of retinal nonperfusion were identified on FA by a distinctive darker appearance of the choroid and the “pruned” appearance indicating closure of retinal vessels in that region. The area of posterior retinal nonperfusion was measured on 7-field FA using the methodology previously described in the SCORE Study Report 9.⁹ A modified EDTRS grid measuring 16 disc areas and composed of 9 subfields (center, inner, and outer) was overlaid electronically on the center of the fovea. The area of retinal nonperfusion in the inner and outer subfields was measured using Image J Version 1.45s (National Institutes of Health, Bethesda, Maryland, USA; available at <http://rsbweb.nih.gov>). The area in the center subfield was considered as the foveal avascular zone and was excluded from the measurement. In the SCORE Study Report 9, an FA was considered ungradable if intraretinal hemorrhage prevented the assessment of retinal nonperfusion within the grid. Similarly, an FA was considered ungradable if it was of poor quality (over-/underexposed or poorly focused) or if the amount of retinal hemorrhage was so great that it prevented any visualization of posterior retinal nonperfusion. If there was presence of intraretinal/retinal hemorrhage as well as visible retinal nonperfusion, the area under the hemorrhage was assumed not to have any retinal nonperfusion unless the hemorrhage was completely surrounded by an area of retinal nonperfusion. To differentiate hemorrhage from any adjacent retinal nonperfusion, an ETDRS grid was placed on the corresponding red-free image and hemorrhages were outlined. Hemorrhages were accurately identified (using the subfield grid lines and vessels as reference markers) and outlined on the FA, and posterior retinal nonperfusion was then measured. In addition to quantitative measurement of posterior retinal nonperfusion, a categorical assessment was done for all FAs from baseline to month 60 to take into consideration retinal nonperfusion outside the central subfields; retinal nonperfusion was graded as none, mild, moderate, severe, or ungradable. A poor-quality image or an image with severe hemorrhage was considered ungradable.

STATISTICAL ANALYSES

Statistical analyses were performed using the Statistical Package for the Social Sciences Version 19 (SPSS Inc, Chicago, Illinois, USA). The Mann-Whitney U test was performed to determine whether there were statistically significant differences between groups with or without severe retinal nonperfusion at year 5 and between groups with VA loss attributable or not attributable to retinal nonperfusion in several parameters: baseline BCVA, peak

BCVA, year 5 BCVA, change in BCVA from baseline to peak, change in BCVA from baseline to year 5, and change in BCVA from peak to year 5. P values were calculated for 2-tailed significance. Relationship between BCVA and area of retinal nonperfusion were assessed using the Spearman rank order correlation (ρ), followed by a linear mixed-effects model using area of retinal nonperfusion stratified by follow-up months.

RESULTS

RESOLUTION OF MACULAR EDEMA WITH INJECTION INDEPENDENCE

Patients were seen every 2 months between month 12 and month 72 and treated with ranibizumab as needed for recurrent/persistent edema, with a goal of achieving resolution of edema without need for ranibizumab injections. Patients were considered to reach this goal of “resolution” when they maintained a substantial amount of their peak improvement in vision and had no evidence of subretinal or intraretinal fluid for at least 6 months after their last injection. If a patient did not resolve by month 40, scatter photocoagulation was given in up to 3 sessions at least 3 months apart, and after the first session focal/grid laser was given to areas of leakage in the macula outside the foveal avascular zone. After resolution, patients were encouraged to remain in the trial, but some patients decided to exit the study after a prolonged period during which no treatment was required (these patients are classified as “reached endpoint and exited trial,” Tables 1 and 2). Some patients withdrew consent prior to resolution of edema; if this occurred prior to month 40 the patient was considered indeterminate with regard to edema resolution and if it occurred after month 40, the patient was considered unresolved.

In patients with BRVO, 8 out of 20 patients completed 6 years of follow-up and 11 completed 5 years; of the latter, 4 had resolution of edema from injections alone, 4 resolved after the addition of laser, and 3 remained unresolved. Of the remaining 9 patients who did not have 5 years of follow-up, 5 resolved before exiting the trial, 1 is unresolved because of withdrawal at month 48 while still requiring injections, and 3 are indeterminate because of withdrawal before month 40. Thus, of the 20 BRVO patients enrolled in the trial, injections alone resulted in resolution in 9 (1 of whom had had grid laser therapy prior to entering the trial) and failed to cause resolution in 8, and 3 were indeterminate (Table 1). In the 9 patients who resolved with injections alone, the mean time from baseline to the last anti-VEGF injection was 20.2 months, the mean number of injections was 6.4, and baseline characteristics showed a mean age, BCVA, and duration of disease of 67.0 years, 24.3 letters, and 16.4 months vs 67.2 years, 21.6 letters, and 14.1 months in the 8 patients who did not resolve from injections alone. Four of the 8 patients who did not resolve from injections alone resolved after scatter and grid laser photocoagulation and an average of 20.8 anti-VEGF injections.

In patients with CRVO, 2 of 10 patients who completed 6 years of follow-up resolved from injections alone and 8 patients failed to resolve, including a patient who no longer needed injections after vitrectomy and laser for recurrent vitreous hemorrhages at month 52 but had a poor visual outcome from severe retinal nonperfusion and was therefore classified as unresolved. None of the other 7 patients resolved after scatter and grid laser therapy. Of the 10 patients who did not complete 6 years of follow-up, 3 resolved before exiting the trial and

7 were indeterminate because they failed to resolve before exiting prior to month 40. Thus, of the 20 CRVO patients enrolled in the trial, injections alone resulted in edema resolution in 5 and failed to cause resolution in 8, and 7 were indeterminate (Table 2). In the 5 patients who resolved, the mean time from baseline to the last anti-VEGF injection was 14.0 months, the mean number of injections was 7.2, and baseline characteristics showed a mean age, BCVA, and duration of disease of 52.8 years, 29 letters, and 4.4 months vs 71.6 years, 19 letters, and 14.4 months in the 8 patients who did not resolve.

PROGRESSION OF RETINAL NONPERFUSION IN PATIENTS WITH RETINAL VEIN OCCLUSION

Measurement of the area of retinal nonperfusion in the central subfields in patients with BRVO who had at least 3 years of follow-up showed that 9 of 14 patients had an increase between their first and last measurement (Figure 1, Upper left). The mean and median area of retinal nonperfusion over time for all patients with BRVO who had gradable FAs at baseline showed little change over the first 3 months, a sharp increase between 3 and 4 months, and then a gradual increase over time (Figure 1, Upper right). Changes in the area of posterior retinal nonperfusion over time were smaller in magnitude in CRVO patients compared with BRVO patients, but like patients with BRVO, the majority (7 of 11) showed an increase between their first and last measurement (Figure 1, Lower left). The mean and median area of retinal nonperfusion over time for CRVO patients who had a gradable FA at baseline showed a decrease between baseline and month 3, a sharp increase between months 3 and 4, and then a slight increase thereafter (Figure 1, Lower right).

Supplemental Figure 1 (available at AJO.com) shows an image from the baseline FA of a patient with a BRVO illustrating retinal nonperfusion superior to the fovea and temporal to the macula. At month 3, there was no change in the retinal nonperfusion superior to the fovea but some reperfusion of previously nonperfused retina temporal to the fovea (Supplemental Figure 2, available at AJO.com). At month 4, 2 months after the last ranibizumab injection, there was an increase in retinal nonperfusion temporal to the fovea (Supplemental Figure 3, available at AJO.com). The patient received 4 anti-VEGF injections between months 4 and 18, trying to minimize injections while maintaining control of edema, and at month 18 there was further worsening of retinal nonperfusion temporal to the fovea (Supplemental Figure 4, available at AJO.com). The patient received 8 injections of ranibizumab between months 18 and 36 with little change in nonperfusion (Supplemental Figure 5, available at AJO.com). Wide-angle fluorescein angiography at month 48 showed very extensive retinal nonperfusion throughout the superior temporal quadrant (Supplemental Figure 6, available at AJO.com) and scatter photocoagulation was done to try to reduce the need for ranibizumab injections. Injections of ranibizumab were still required at every visit (about every 2 months) and supplemental scatter and grid laser were given at month 56. At month 66, there was less leakage but edema was still present (Supplemental Figure 7, available at AJO.com). Despite the many episodes of recurrent edema and lack of stability at M72, visual outcome was excellent (Supplemental Figure 8, available at AJO.com).

Supplemental Figure 9 (available at AJO.com) shows an image from the baseline FA of a 66-year-old patient with an 18-month history of CRVO. There is widening of the foveal avascular zone and areas of retinal nonperfusion throughout the posterior pole. After 3 injections of ranibizumab, there was less retinal nonperfusion (Supplemental Figure 10, available at AJO.com). Ten anti-VEGF injections were given between months 4 and 36 to try and manage edema while minimizing the number of injections and at month 36 there was a substantial increase in posterior retinal nonperfusion (Supplemental Figure 11, available at AJO.com). A wide-angle FA at month 46 showed extensive retinal nonperfusion throughout the periphery (Supplemental Figure 12, available at AJO.com) and scatter photocoagulation was done throughout the periphery anterior to the equator (Supplemental Figure 13, available at AJO.com), after which recurrent edema seemed less severe, although injections of ranibizumab were still required at most visits through month 72 (Supplemental Figure 14, available at AJO.com).

Patients with BRVO who did not have at least 5 years of follow-up provided little information regarding change in retinal nonperfusion over time because of insufficient assessments, but their gradings are shown for completeness (Figure 2, Top). One had severe retinal nonperfusion at baseline that decreased to moderate at months 3 and 4 and then increased to severe at months 24 and 36. In the 11 patients with BRVO who completed at least 5 years of follow-up, posterior retinal nonperfusion at baseline was severe in 3, moderate in 3, mild in 2, none in 1, and not gradable in 2 (Figure 2, Bottom). The 2 patients with ungradable FAs at baseline had no retinal nonperfusion on their first gradable FA. At month 60, all patients who had severe or moderate retinal nonperfusion and 1 who had mild retinal nonperfusion at baseline had severe retinal nonperfusion, while the 4 remaining patients had no or mild retinal nonperfusion on their first gradable FA and at month 60. One patient who had severe retinal nonperfusion at baseline showed additional worsening of retinal nonperfusion between baseline and month 60 and 1 patient with no retinal nonperfusion on the first gradable FA had mild retinal nonperfusion at month 60. Thus, 54.5% of patients showed an increase in retinal nonperfusion category over the course of 5 years. Patients who had little or no retinal nonperfusion at baseline appeared less likely to progress, but the number of patients evaluated was too small to make any firm conclusions.

At baseline in the 10 patients with CRVO who completed at least 5 years of follow-up, retinal nonperfusion was moderate in 2, mild in 4, none in 1, and not gradable in 3 (Figure 3). The patients who were not gradable at baseline had mild retinal nonperfusion on their first gradable FA. The 2 patients with moderate retinal nonperfusion at baseline and 1 with mild retinal nonperfusion on the first gradable FA progressed to severe retinal nonperfusion by month 60; the remaining 7 patients had mild or no retinal nonperfusion at month 60. In addition to the 3 patients who changed categories, 2 patients showed a definite increase in retinal nonperfusion but still fell within the mild retinal nonperfusion category at month 60, and therefore 50% of patients had worsening of retinal nonperfusion.

EFFECT OF WORSENING RETINAL NONPERFUSION ON VISUAL ACUITY

Among patients who completed at least 5 years of follow-up, 3 with BRVO and 2 with CRVO had a reduction in BCVA that was directly attributable to worsening of retinal

nonperfusion (a third patient with CRVO who died at month 38 also experienced severe loss of vision from progression of retinal nonperfusion, Table 2). Supplemental Figure 15 (available at AJO.com) shows an image from the baseline FA of an 82-year-old man with BRVO for 15 months. There was substantial retinal nonperfusion temporal to the fovea. After 3 injections of ranibizumab, there was improvement in retinal nonperfusion (Supplemental Figure 16, available at AJO.com), but at month 4, 2 months after the last ranibizumab injection, the previously reperfused vessels were closed (Supplemental Figure 17, available at AJO.com). Between months 4 and 18, BCVA dropped with recurrent edema and improved after injection of ranibizumab, but FA at month 18 showed nasal extension of retinal nonperfusion to involve the entire perifoveal capillary bed (Supplemental Figure 18, available at AJO.com), and after that point BCVA did not improve to the former levels when macular edema was controlled. At month 36, there was further progression of retinal nonperfusion with closure of some large vessels (Supplemental Figure 19, available at AJO.com). Supplemental Figure 20 (available at AJO.com) shows a frame from a wide-angle FA after scatter photocoagulation at months 42 and 46, which did not eliminate the need for ranibizumab injections at each study visit through month 72 (Supplemental Figure 21, available at AJO.com). Supplemental Figure 22 (available at AJO.com) shows FA frames from a 78-year-old woman with CRVO after 3 injections of ranibizumab; there are hemorrhages, but no definite retinal nonperfusion. The next FA at month 18 shows severe retinal nonperfusion (Supplemental Figure 23, available at AJO.com) with further worsening at month 36 (Supplemental Figure 24, available at AJO.com). A plot of the patient's BCVA over time shows that the BCVA dropped precipitously between months 9 and 12 and never recovered (Supplemental Figure 25, available at AJO.com), suggesting that ischemic damage to the macula contributed to the permanent reduction in BCVA.

Table 3 shows baseline, peak, and month 60 BCVA in BRVO with at least 5 years of follow-up. Peak improvements from baseline ranged from 11–37 letters with a mean of 22.1 (Table 4) and improvement 20 letters in 8 of 11 patients (Table 3). At month 60, change from baseline ranged from –20 to +30 letters with a mean of 12.5. The mean change from baseline to peak visual acuity was similar in the 3 patients that ultimately lost vision because of retinal nonperfusion and the other 8 patients (19.7 vs 23.0 letters), but at month 60 they showed worsening from baseline (–1.3 letters) compared to mean improvement of 17.6 letters ($P < .05$) in the other 8 patients. The Spearman correlation coefficient between BCVA and area of posterior retinal nonperfusion was –0.667 ($P < .05$) at baseline, –0.564 ($P < .05$) at months 18 and 24, and –0.693 ($P < .02$) at month 36 (Table 5). The correlation coefficient by linear mixed-effects model was not significant.

Table 6 shows baseline, peak, and month 60 BCVA in patients with CRVO. Peak improvements from baseline ranged from 13–31 letters with a mean of 20.8 letters (Table 7) and improvement 15 letters in 8 of 10 patients (Table 6). At month 60, change from baseline ranged from –17 to +27 letters with a mean of 9.8. The 3 patients with severe retinal nonperfusion at month 60 had reduced BCVA at baseline compared to the other 7 patients (36.3 vs 55.3 letters), but change from baseline to peak visual acuity was similar (21.7 vs 20.4 letters). However, the 3 patients with severe retinal nonperfusion at month 60 had a mean improvement between baseline and month 60 of 6.7 letters vs 11.2 letters in the

other 7 patients. The Spearman correlation coefficient between BCVA and area of posterior retinal nonperfusion showed a significant negative correlation at month 4 and beyond (Table 8). The model showed that at month 4, there was an associated drop of around 7 letters per increase in disc area of retinal nonperfusion, which did not change when adjusted for macular thickness ($P < .01$). After month 4, an increase in disc area of retinal nonperfusion was associated with a drop of around 6 letters, which when adjusted for macular thickness was associated with a drop of 3–4 letters ($P < .05$).

EFFECT OF SCATTER PHOTOCOAGULATION

Seven of 11 patients with BRVO were treated with laser, with a mean duration of 63.7 months between vein occlusion and onset of laser treatment (Table 1). The average time of follow-up after completion of laser treatments was 17.2 months. Patient B15 showed no definite change in amount of edema, visual acuity, or need for injections following laser. Patient B06 had elimination of edema and improvement in vision with no injections required for 9 months at last follow-up (Supplemental Figure 26, available at [AJO.com](http://ajoc.com)). After completing laser, Patient B10 had 4 additional ranibizumab injections but has not required additional injections for 6 months and has resolution of edema. Patient B18 had a possible improvement with a decrease in the number of injections required and stabilization of vision following laser. Patient B20 received a single laser at month 60 and required no ranibizumab injections through month 72. Patient B14 had a worsening of edema following laser that was not responsive to anti-VEGF treatment. Patient B11 had a transient drop in vision that gradually recovered. Thus, while laser may have helped to stabilize 4 patients, it caused a transient worsening in some patients and little identifiable long-term effect in 3 patients.

Eight of 10 patients with CRVO were treated with laser, with a mean duration of 60 months between vein occlusion and laser treatment (Table 2). The average time of follow-up after completion of laser treatments was 14.3 months. Five patients (C05, C08, C15, C17, C18) had no definite change in amount of edema, visual acuity, or need for injections following laser treatment. Two patients were severely ischemic; laser treatment did not reduce the need for injections in Patient C10 and Patient C09 no longer needed injections after vitrectomy and laser treatment but had a poor visual outcome. Patient C11 had good vision with modest edema prior to scatter photocoagulation and after-ward there was an increase in edema and reduced vision that over time, with many additional ranibizumab injections, improved almost back to the pre-laser level.

DISCUSSION

In the current study, initiated prior to bravo and CRUISE, patients with BRVO or CRVO were treated with 3 injections of ranibizumab followed by an attempt between months 3 and 12 to minimize treatment (rescue treatments allowed for decreased BCVA 5 letters from previous visit) to determine if edema would resolve spontaneously after initial recurrence. When it became clear that this did not occur in most patients, the protocol was amended and after month 12, patients were evaluated every 2 months and given an injection of ranibizumab if there was recurrent/persistent edema. We have previously reported beneficial effects of ranibizumab at the 3-month primary endpoint¹ and partial maintenance of those

benefits through 24 months with intermittent injections of ranibizumab.⁶ Our expectation was that patients would maintain visual gains and gradually require fewer injections, and eventually have resolution of edema. This occurred in 45% of BRVO patients after a mean of 6.4 injections over 20.2 months, failed to occur within a span of at least 40 months in 40%, and was indeterminate in 15% who exited the trial prior to month 40 without edema resolution. Resolved patients did not differ from those that failed to resolve in baseline characteristics including age, duration of disease, or BCVA. Of the 8 patients who still required ranibizumab injections to control edema after month 40, 4 stabilized after scatter and grid laser photocoagulation and thus 65% no longer required ranibizumab injections at month 72.

The situation was different for patients with CRVO, for whom only 25% had resolution of edema after a mean of 7.2 injections over 14.0 months, 40% failed to resolve within 40 months, and 35% were indeterminate because they left the trial before month 40 without edema resolution. Compared to patients who did not resolve with injections alone, those that resolved differed in baseline characteristics in that they were younger (52.8 vs 71.6 years old), had shorter duration of disease (4.4 vs 14.4 months), and had better BCVA (29 vs 19 letters). Because of the small numbers involved, these differences may be attributable to chance, but they provide important leads for future studies. None of 9 patients who did not resolve from injections alone had resolution of edema after laser photocoagulation (1 patient no longer needed injections after vitrectomy and extensive laser for recurrent vitreous hemorrhages, but had a poor visual outcome that precludes categorization as resolved), and thus 30% no longer required ranibizumab. The mean number of anti-VEGF injections given in the 8 patients who failed to resolve with injections alone was 28.3 at month 72.

In addition to possible differences in baseline characteristics listed above for patients with CRVO, another possible contributor to the failure of at least 40% of BRVO and CRVO patients to stabilize after 40 months of intermittent injections of ranibizumab was progressive retinal nonperfusion. Analysis of fluorescein angiograms in patients participating in the BRAVO and CRUISE studies showed that patients in the sham group had progression of retinal nonperfusion between baseline and month 6, which did not occur in the ranibizumab treatment groups, indicating that monthly injections of ranibizumab prevent worsening of retinal nonperfusion.¹⁰ In the current study we found that our treatment regimen, which was designed to give the fewest number of injections of ranibizumab to control edema, was not sufficient to prevent progression of retinal nonperfusion. In 3 patients with BRVO and 3 patients with CRVO, progression of retinal nonperfusion resulted in severe loss of vision. There was a negative correlation between amount of posterior retinal nonperfusion and BCVA for patients who completed 5 years of follow-up, and there was a substantial decline from mean peak BCVA to mean BCVA at month 60, owing in part to progression of retinal nonperfusion. It is likely that progression of retinal nonperfusion, which is an indicator of worsening retinal ischemia, also contributed to the inability of many patients to achieve resolution of edema, because there was a trend for progression of nonperfusion to be more common in unresolved vs resolved patients. Once again, because of the small number of patients involved, it is possible that this is a chance occurrence; however, it is a potentially important finding that must be evaluated in future long-term follow-up studies of patients with RVO. In view of the progression of

retinal nonperfusion and its association with poor outcomes, it was hypothesized that scatter photocoagulation would promote resolution of edema. The combination of scatter and grid photocoagulation led to edema resolution in 4 of 8 patients with BRVO, but it is unknown if this was simply attributable to the grid laser, which is known to reduce edema in patients with BRVO,¹¹ or whether scatter photocoagulation also contributed. In patients with CRVO, there was little evidence that scatter photocoagulation initiated at least 40 months after beginning treatment with anti-VEGF injections reduced the need for injections with a mean follow-up of about 14 months after completion of the laser. After laser treatment, residual leakage on FAs was often reduced and seemed to occur from telangiectatic vessels in the macula, which may represent vessels that have become structurally altered from chronic ischemia. Therefore, we cannot rule out the possibility that scatter photocoagulation earlier in the course of RVO would provide benefit and help to prevent the progression of retinal nonperfusion that was observed, but we can say that scatter photocoagulation after several years of ischemia and persistent/ recurrent macular edema provides little obvious benefit in patients with CRVO.

In summary, anti-VEGF injections no more frequently than every 2 months for recurrent/ persistent edema do not cause ultimate resolution of edema and injection independence in most patients with RVO. In patients with CRVO, those who stabilize with injections alone tended to be younger and have better BCVA at onset of anti-VEGF injections, suggesting that there may be 2 distinct populations of patients with CRVO. A critical observation in our study is that progression of retinal nonperfusion is not prevented by anti-VEGF injections only as frequently as every 2 months, and it correlates with reduction in BCVA over time. These data suggest that treatment of recurrent/persistent edema is not the only objective of anti-VEGF treatment, but rather a second objective is to prevent worsening of retinal nonperfusion. This may require more aggressive treatment strategies (ideally, some type of sustained delivery) and periodic fluorescein angiograms to monitor perfusion status, but may also safeguard visual benefits and promote long-term stability. Additional studies are needed to test this hypothesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Change in area of posterior retinal nonperfusion over time in patients with branch retinal vein occlusion (BRVO, Top row) or central retinal vein occlusion (CRVO, Bottom row). (Top left) The area of retinal nonperfusion in the inner and outer subfields on each gradable fluorescein angiogram is plotted between baseline and month 36 in patients with BRVO. (Top right) Mean and median area of retinal nonperfusion for BRVO patients with a gradable fluorescein angiogram at baseline. (Bottom left) The area of retinal nonperfusion in the inner and outer subfields on each gradable fluorescein angiogram is plotted between

baseline and month 36 in patients with CRVO. (Bottom right) Mean and median area of retinal nonperfusion for CRVO patients with a gradable fluorescein angiogram at baseline.

Patients without Five Years of follow up

ID	BL	M3	M4	M18	M24	M30	M36	M48	M60
B08	None	None	None	None	None		None		
B19	Mild	Mild	Mild						
B03	Mild	Mild	Mild	Mild					
B07	Mild	Mild	Mild	Mild					
B16	NG	None	Mild	Mild	Mild				
B04	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	
B05	Mod	Mod	Mod	Mild	Mild		Mild		
B02	NG	Mild	Mod						
B01	Severe	Mod	Mod		Severe		Severe		

Patients with Five Years of follow up

B13	None	None	None	None	None	None	None	None	None
B11	NG	NG	None	None	None	None	None	None	None
B09	NG	None	NG	Mild	Mild	Mild	Mild	Mild	Mild
B17	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild
B10	Mild	Mild	Mild	Mod	Mod	Mod	Mod	Severe ⁺⁺	Severe
B06	Mod	Mod	Mod	NG	Mod	Mod	Mod	Severe ⁺	Severe
B15	Mod	Mild	Mod	Mod	Mod	Mod	Mod	Severe	Severe
B14	Mod	NG	Mod	Severe	Severe	Severe	Severe	Severe ⁺	Severe
B12	Severe	Mild	Mod	Severe	Severe	Severe	Severe	Severe	Severe
B18	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe ⁺⁺⁺
B20	Severe	Severe	NG	Severe	Severe	NG	Severe	Severe	Severe

Figure 2.

Grading of retinal nonperfusion on fluorescein angiograms of branch vein occlusion patients. (Top) Categorical grading of retinal nonperfusion in patients without 5-year follow-up. (Bottom) Categorical grading of retinal nonperfusion in patients with 5-year follow-up. BL = baseline; M = month; NG = nongradable; Mod = moderate.

Patients without Five Years of follow up

ID	BL	M3	M4	M18	M24	M30	M36	M48	M60
C14	None								
C04	None	None	None						
C13	Mild	Mild	Mild	None	None	None	None		
C03	Mild	Mild	Mild						
C12	Mild	Mild	Mild						
C01	Mild	Mild	Mild	Mild					
C06	Mild		Mild	Mild					
C02	Mod			Mod					
C20	Severe	Mod	Mod						
C07	Mild	Mild	Mod	Severe	Severe				

Patients with Five Years of follow up

C17	None	None	None	None	None	None	None	None	None
C19	Mild	None	None	None	None	None	None	None	None
C05	Mild	None	Mild	Mild	Mild	Mild	Mild	Mild	Mild
C08	Mild	None	Mild	NG	None	NG	Mild	Mild	Mild
C11	Mild	None	Mild	Mild	Mild	Mild	Mild	Mild	Mild
C16	NG	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild
C18	NG	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild
C10	NG	Mild	NG	Severe	Severe	Severe	Severe	Severe	Severe
C15	Mod	Mild	Mod	Mod	Severe	Severe	Severe	Severe ⁺	Severe
C09	Mod	Mild	Mod	Severe	Severe	Severe	Severe	NG	Severe

Figure 3.

Grading of retinal nonperfusion on fluorescein angiograms of central vein occlusion patients. (Top) Categorical grading of retinal nonperfusion in patients without 5-year follow-up. (Bottom) Categorical grading of retinal nonperfusion in patients with 5-year follow-up. BL = baseline; M = month; NG = nongradable; Mod = moderate.

TABLE 1

Disposition and Stability Status of Branch Retinal Vein Occlusion Patients

Patient ID	BCVA at Baseline (ETDRS Letter Score (Snellen Equivalent))	BCVA at Last Visit (ETDRS Letter Score (Snellen Equivalent))	CST at Last Visit (mm)	Follow-up Period (Months)	Last Injection (Month)	Time for Assessing Stability (Months)	Stability Assessment	Total Number of Anti-VEGF Injections	Status
B01	32 (20/250)	70 (20/40)	197	48	2	46	S	3	Reached endpoint and exited trial
B02	30 (20/250)	65 (20/50)	168	12	2	10	CD	3	Withdrew consent
B03	51 (20/100)	60 (20/63)	207	58	34	24	S	5	Developed NVAMD at M58
B04	66 (20/50)	67 (20/50)	284	48	48	0	NS	12	Withdrew consent -laser M48
B05	35 (20/200)	73 (20/32)	168	38	2	36	S	3	Reached endpoint and exited trial
B06	49 (20/100)	75 (20/32)	229	72	63	9	SL	27	Laser M48, M52, M60
B07	61 (20/63)	68 (20/50)	416	9	2	7	CD	3	Withdrew consent
B08	67 (20/50)	63 (20/50)	233	48	20	28	S	5	Reached endpoint and exited trial
B09	62 (20/63)	83 (20/20)	220	60	32	28	S	13	Reached endpoint and exited trial
B10	61 (20/63)	80 (20/25)	180	72	66	6	SL	29	Laser M48, M56
B11	39 (20/160)	73 (20/32)	229	72	70	2	NS	30	Laser M48
B12	50 (20/100)	61 (20/63)	184	72	22	28	S	6	Reached endpoint and exited trial
B13	56 (20/80)	64 (20/50)	240	72	34	38	S	15	Stable
B14	34 (20/200)	38 (20/160)	573	72	72	0	NS	32	Laser M4, M46
B15	65 (20/50)	65 (20/50)	215	63	60	3	NS	18	Laser M52, M56, M60
B16	65 (20/50)	79 (20/25)	232	42	34	8	S	5	Deceased
B17	71 (20/40)	89 (20/16)	180	72	2	70	S	3	Stable
B18	39 (20/160)	53 (20/125)	193	72	54	18	SL	18	Lost vision due to RNP, laser M44
B19	58 (20/80)	69 (20/40)	215	4	2	2	CD	3	Withdrew consent
B20	60 (20/63)	68 (20/40)	255	72	60	12	SL	9	Severe RNP, laser M60

BCVA = best-corrected visual acuity; CD = cannot determine; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; M = month; NS = not stable; NVAMD = neovascular age-related macular degeneration; RNP = retinal nonperfusion; S = stable; SL = stable after laser; VEGF = vascular endothelial growth factor.

TABLE 2

Disposition and Stability Status of Central Retinal Vein Occlusion Patients

Patient ID	BCVA at Baseline (ETDRS Letter Score (Snellen Equivalent))	BCVA at Last Visit (ETDRS Letter Score (Snellen Equivalent))	CST at Last Visit (mm)	Follow up Period (Months)	Last Injection (Month)	Time for Assessing Stability (Months)	Stability Assessment	Total Number of Anti-VEGF Injections	Status
C01	38 (20/160)	47 (20/125)	390	22	20	2	CD	6	Lost to follow-up
C02	32 (20/250)	50 (20/100)	172	2	2	0	CD	3	Withdrew consent
C03	33 (20/200)	43 (20/125)	278	6	6	0	CD	4	Deceased
C04	70 (20/40)	85 (20/20)	241	12	1	11	S	2	Reached endpoint and exited trial
C05	34 (20/200)	38 (20/160)	348	72	72	0	NS	29	Laser M48, M54, M64
C06	48 (20/100)	89 (20/16)	199	44	6	38	S	4	Reached endpoint and exited trial
C07	50 (20/100)	26 (20/320)	203	30	24	6	CD	10	Deceased-lost vision due to RNP
C08	58 (20/80)	67 (20/50)	280	72	72	0	NS	33	Laser M48, M54, M67
C09	19 (20/400)	36 (20/200)	152	72	43	29	NS	13	Laser M32, vitrectomy and laser M52
C10	37 (20/200)	30 (20/250)	489	72	72	0	NS	39	Laser M48, M54
C11	54 (20/80)	71 (20/40)	352	72	72	0	NS	33	Laser M48, M54, M63
C12	25 (20/320)	42 (20/160)	565	4	4	0	CD	5	Withdrew consent
C13	62 (20/63)	72 (20/32)	175	50	34	16	S	14	Reached endpoint and exited trial
C14	69 (20/40)	61 (20/63)	433	6	2	4	CD	2	Withdrew consent
C15	53 (20/80)	75 (20/32)	176	72	72	0	NS	26	Laser M46, M66
C16	49 (20/100)	64 (20/50)	146	72	26	46	S	12	Stable
C17	64 (20/50)	74 (20/32)	243	72	69	3	NS	20	Laser M46, M54
C18	62 (20/63)	62 (20/63)	271	72	72	0	NS	33	Laser M42, M46
C19	66 (20/50)	90 (20/16)	202	72	3	69	S	4	Stable
C20	48 (20/125)	60 (20/63)	193	6	2	4	CD	3	Withdrew consent

BCVA = best-corrected visual acuity; CD = cannot determine; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; M=month; NS = not stable; RNP = retinal nonperfusion; S = stable; SL = stable after laser; VEGF = vascular endothelial growth factor.

TABLE 3

Best Corrected Visual Acuity Parameters and Attribution of Best Corrected Visual Acuity due to Retinal Non Perfusion for All Branch Retinal Vein Occlusion Patients

ID	BL BCVA	Peak BCVA	Year 5 BCVA	DBCVA-BL to Peak	DBCVA-BL to Year 5	DBCVA-Peak to Year 5	Decrease in BCVA attributed to RNP	Number of Anti-VEGF Injections given
B13	56	74	64	18	8	-10	No	15
B11	39	76	69	37	30	-7	No	22
B09	62	83	83	21	21	0	No	13
B17	71	92	86	21	15	-6	No	17
B10	61	81	74	20	13	-7	No	27
B06	49	73	67	24	18	-6	No	27
B15	65	76	45	11	-20	-31	Yes	17
B14	34	59	41	25	7	-18	Yes	26
B12	50	73	59	23	9	-14	Yes	6
B18	39	67	61	28	22	-6	No	18
B20	60	75	74	15	14	-1	No	22

BL = baseline; BCVA = best corrected visual acuity; RNP = retinal non perfusion; VEGF = vascular endothelial growth factor.

TABLE 4

Effect of Severe Retinal Non Perfusion and Retinal Non Perfusion Progression Associated Visual Acuity Loss on Best Corrected Visual Acuity Parameters in Branch Retinal Vein Occlusion Patients

	BL BCVA	Peak BCVA	Year 5 BCVA	BCVA-BL to Peak	BCVA-BL to Year 5	BCVA-Peak to Year 5
All patients (n= 11)	53.3	75.4	65.7	22.1	12.5	-9.6
Patients with severe RNP at Year 5 (n=7)	51.1	72.0	60.1	20.9	9.0	-11.9
Patients without severe RNP at Year 5 (n=4)	57.0	81.3	75.5	24.3	18.5	-5.8
Patients whose VA loss is attributed to RNP progression (n=3)	49.7	69.3	48.3*	19.7	-1.3*	-21.0*
Patients whose VA loss is not attributed to RNP progression (n=8)	54.6	77.6	72.3*	23.0	17.6*	-5.4*

BL = baseline; BCVA = best corrected visual acuity; RNP = retinal non perfusion; VA = visual acuity.

* $P < 0.05$.

TABLE 5
Correlation of Area of Posterior Retinal Non Perfusion with Best Corrected Visual Acuity in Branch Retinal Vein Occlusion Patients

	Baseline	Month 3	Month 4	Month 18	Month 24	Month 36
Spearman Correlation Coefficient	-.667*	-.537	-.511	-.564	-.564*	-.693*
<i>P</i> value	0.04	0.06	0.06	0.05	0.04	0.02
Unadjusted Coefficient	-0.790	-1.023	-0.415	-1.306	-0.290	-0.632
<i>P</i> value	0.14	0.09	0.32	0.06	0.36	0.22
Adjusted Coefficient controlling for central subfield thickness	-0.827	-1.029	-0.427	-1.293	-0.275	-0.641
<i>P</i> value	0.13	0.09	0.32	0.06	0.40	0.22

* $P < 0.05$.

The unadjusted and adjusted coefficients are from linear mixed effects model using retinal non perfusion stratified by follow-up months as the predictors. A random intercept is used for individual patients to account for the repeated measures from the same patient at different visits.

TABLE 6

Best Corrected Visual Acuity Parameters and Attribution of Best Corrected Visual Acuity due to Retinal Non Perfusion for all Central Retinal Vein Occlusion Patients

ID	BL BCVA	Peak BCVA	Year 5 BCVA	BCVA-BL to Peak	BCVA-BL to Year 5	BCVA-Peak to Year 5	Decrease in BCVA attributed to RNP	Number of Anti-VEGF Injections given
C17	64	79	74	15	10	-5	No	13
C19	66	94	93	28	27	-1	No	3
C05	34	52	25	18	-9	-27	No	25
C08	58	76	66	18	8	-10	No	28
C11	54	85	75	31	21	-10	No	27
C16	49	69	66	20	17	-3	No	12
C18	62	75	66	13	4	-9	No	30
C10	37	62	20	25	-17	-42	Yes	31
C15	53	72	72	19	19	0	No	22
C09	19	40	37	21	18	-3	Yes	13

BL = baseline; BCVA = best corrected visual acuity; RNP = retinal non perfusion; VEGF = vascular endothelial growth factor.

TABLE 7

Effect of Severe Retinal Non Perfusion and Retinal Non Perfusion Progression Associated Visual Acuity Loss on Best Corrected Visual Acuity Parameters in Central Retinal Vein Occlusion Patients

	BL BCVA	Peak BCVA	Year 5 BCVA	BCVA-BL to Peak	BCVA-BL to Year 5	BCVA-Peak to Year 5
All patients (n= 10)	49.6	70.4	59.4	20.8	9.8	-11.0
Patients with severe RNP at year 5 (n=3)	36.3	58.0	43.0	21.7	6.7	-15.0
Patients without severe RNP at year 5 (n=7)	55.3	75.7	66.4	20.4	11.2	-9.3
Patients whose VA loss is attributed to RNP progression (n=2)	28.0	51.0	28.5	23.0	0.5	-22.5
Patients whose VA loss is not attributed to RNP progression (n=8)	55.0	75.3	67.1	20.3	12.2	-8.1

BL = baseline; BCVA = best corrected visual acuity; RNP = retinal non perfusion; VEGF = vascular endothelial growth factor; VA = visual acuity.

TABLE 8
Correlation of Area of Posterior Retinal Non Perfusion with Best Corrected Visual Acuity Central Retinal Vein Occlusion Patients

	Baseline	Month 3	Month 4	Month 18	Month 24	Month 36
Spearman Correlation Coefficient	-.429	-.511	-.879*	-.837*	-.790*	-.741*
<i>P</i> value	0.17	0.07	.001	.003	0.01	0.02
Unadjusted Coefficient	-3.524	-6.054	-7.210*	-5.830*	-6.693*	-5.723*
<i>P</i> value	0.17	0.06	0.01	<.001	<.001	<.001
Adjusted Coefficient controlling for central subfield thickness	0.847	-3.281	-6.691*	-2.997*	-3.950*	-3.909*
<i>P</i> value	0.39	0.13	0.001	0.02	0.003	<.001

* $P < 0.05$.

The unadjusted and adjusted coefficients are from linear mixed effects model using retinal non perfusion stratified by follow-up months as the predictors. A random intercept is used for individual patients to account for the repeated measures from the same patient at different visits.