

Response of Retinal Vessels and Retrobulbar Hemodynamics to Intravitreal Anti-VEGF Treatment in Eyes with Branch Retinal Vein Occlusion

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PURPOSE. To investigate whether intravitreal ranibizumab (0.05 mL) treatment affects retinal vessel diameters and retrobulbar blood velocities in patients with acute branch retinal vein occlusion (BRVO).

METHODS. Thirty patients with clinically significant macular edema secondary to BRVO were included. The duration of the study was three months. Patients were studied before and one week, one month, two months, and three months after the first ranibizumab injection. Depending on the clinical requirements, up to three ranibizumab injections were administered. Retinal vessel diameters were measured using a retinal vessel analyzer. Flow velocities in the retrobulbar central retinal artery were measured using color doppler imaging. Best-corrected visual acuity was assessed using ETDRS charts. Measurements were done in the affected as well as in the contralateral eye.

RESULTS. Three patients were lost for follow up. In the remaining 27 patients, significant vasoconstriction was observed in retinal veins ($P < 0.001$ versus baseline) and in retinal arteries ($P = 0.001$ versus baseline) of the affected eyes. In addition, a significant reduction in flow velocities was observed in the BRVO eyes over time (peak systolic velocity: $P = 0.003$, end diastolic velocity: $P = 0.003$). The reduction in retinal vessel diameters and flow velocities did not correlate with changes in visual acuity or number of re-treatments. In the contralateral eyes no change in retinal blood flow parameters was seen.

CONCLUSIONS. BRVO is an ischemic retinal disease. Given that ranibizumab treatment reduces retinal perfusion in these eyes the potential long-term effects of this vasoconstriction need to be considered. (ClinicalTrials.gov number, NCT01027481.) (*Invest Ophthalmol Vis Sci.* 2011;52:3046-3050) DOI:10.1167/iov.10-5842

Branch retinal vein occlusion (BRVO) is commonly seen in clinical practice and can be a cause of significant visual impairment. The most common complication and the leading cause of visual loss is macular edema, which has

been found in 58-100% of cases, and persists in two out of three cases.¹⁻³ The most common cause of a BRVO is the compression of the branch vein at an arteriovenous crossing by the adjacent branch artery, which causes increased intravascular hydrostatic pressure and results in secondary macular edema that, in turn, is associated with severe vision loss.⁴⁻⁶

Although numerous procedures, including medical therapy with anticoagulants, fibrinolytics, corticosteroids, acetazolamide, and isovolemic hemodilution have been proposed, the evidence for these therapies to improve visual outcome is poor.^{7,8} Laser therapies include panretinal and grid pattern lasercoagulation, with moderate success in stabilizing visual acuity.⁹ Finally, surgical interventions have been proposed, including vitrectomy, surgically induced chorioretinal anastomosis, and direct venous cannulation with injection of fibrinolytics, but again the evidence for these interventions is poor.¹⁰ Intravitreal injection of triamcinolone acetonide, a long-acting corticoid derivative, led to a significant improvement in mean VA in patients with macular edema due to BRVO.¹¹ The recent SCORE study, however, showed that 12 months' triamcinolone treatment was not better than grid laser treatment, but induced more side effects.¹²

Greater understanding of the pathophysiology of macular edema has provided a scientific rationale for the use of anti vascular endothelial growth factor (VEGF) drugs as a potential treatment. VEGF is expressed at increased concentrations in the setting of macular edema. It is a potent promoter of vascular permeability. Most recently, intravitreal administration of anti-VEGF drugs has gained much interest and the results are promising.^{13,14}

In a previous study,¹⁵ we showed that the early retinal venous vasoconstriction after grid photocoagulation in BRVO is closely correlated to the visual outcome after three months. This indicates that the BRVO retina is less hypoxic after grid photocoagulation, because hypoxia is a potent vasodilator in retinal vessels.¹⁶⁻¹⁸ This could be of clinical importance, because the degree of vasoconstriction might be an early marker of treatment success, compatible with the idea that hypoxia is the major trigger of VEGF in BRVO. The present study evaluated the response of retinal vessel diameters and the effect on retrobulbar blood velocities to anti-VEGF treatment with ranibizumab (Lucentis; Novartis, Basel, Switzerland) in patients with BRVO. This was done in an effort to gain insight into the retinal hemodynamic consequences of anti-VEGF treatment in BRVO. The hypothesis that anti-VEGF treatment is associated with a vasoconstrictor response in retinal vessels in patients with BRVO was tested.

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MATERIALS AND METHODS

Study Design and Patients

We performed an open, interventional clinical study over a period of three months. Thirty patients scheduled for intravitreal anti-VEGF treatment with significant macular edema secondary to BRVO were included. The study protocol was approved by the Ethics Committee of the Medical University of Vienna and followed the guidelines of Good Clinical Practice and the Declaration of Helsinki. All patients signed a written informed consent to participate. Subject eligibility based on visual acuity, ophthalmic examination, and fluorescein angiography was evaluated at the first visit.

Main inclusion criteria were the confirmed diagnosis of untreated acute BRVO and a decrease of visual acuity due to significant macular edema ($>300 \mu\text{m}$ measured by spectral domain technology [Cirrus OCT; Carl Zeiss Meditec, Jena, Germany) involving the foveal center. All patients were examined for internal risk factors by an internal medicine physician within two to four weeks after the first ophthalmic examination. Patients were not enrolled in the study if spontaneous recovery of macular edema and improvement in vision were observed during this examination. The duration of symptoms before inclusion ranged between one and three months.

Exclusion criteria were history of glaucoma, aphakia or presence of an anterior chamber intraocular lens, signs of non-perfusion or ischemia (neovascularization, rubeosis iridis), significant cataract, ocular infections, any history of retinal disease other than BRVO (i.e., signs of age-related macular degeneration, diabetic retinopathy, macular edema for other reasons than BRVO, or previous vitreoretinal surgery), and other ocular conditions that could prevent a 15-letter improvement in visual acuity (e.g., severe macular ischemia).

All patients who met the eligibility criteria received intravitreal application of 0.05 mL ranibizumab (0.05 mg Lucentis; Novartis) at the treatment day. The treatment was repeated if either an increase in central retinal thickness ($>50 \mu\text{m}$ compared to last visit) or a decrease in best-corrected visual acuity (BCVA > 5 letters) associated with the presence of macular edema was evident. Re-treatments were done in monthly intervals.

All patients underwent standardized ophthalmic examinations according to the protocol at baseline, weeks 1, 4, 8, and 12 after initial treatment. The examinations included measurement of BCVA using ETDRS chart at a distance of two meters, measurement of intraocular pressure (IOP), slit-lamp examination, ophthalmoscopy, evaluation of retinal arterial and venous diameters using a retinal vessel analyzer (RVA; Imedos, Jena, Germany), and blood flow velocities in the central retinal artery (CRA) as measured with color Doppler imaging (CDI). IOP was measured with an applanation tonometer (Goldmann; Haag-Streit, Vienna, Austria) at each scheduled visit.

Noninvasive Measurement of Systemic Hemodynamics

Systolic, diastolic, and mean arterial pressure (MAP) were measured on the upper arm using an automated oscillometric device. Pulse rate was automatically recorded from a finger pulse-oxymetric device (HP-CMS patient monitor; Hewlett Packard, Palo Alto, CA).

Retinal Vessel Analyzer

The RVA (Imedos) is a commercially available system consisting of a fundus camera, a video camera, a high-resolution video recorder, a real-time monitor, and a personal computer with a vessel diameter analyzing software. The RVA allows for a precise determination of retinal vessel diameter with a time resolution of 25 readings per second. The fundus is illuminated with light in the range of wavelengths between 567 nm and 587 nm. In this spectral range, the contrast between retinal vessels and the surrounding tissue is optimal. Retinal irradiance was approximately $220 \mu\text{W}/\text{cm}^2$, which is 50 times lower than the maximum level allowed for constant illumination of the retina at the wavelengths mentioned. The system provides excellent reproducibility and sensitivity.^{19,20} In the present study, major tempo-

ral arteries and veins were studied. Measurements of retinal arterial and venous diameters were taken between 1 and 2 disc diameters from the margin of the optic disc. Measurements were done in non-affected temporal quadrants of the retina. Measurements were taken for 90 to 120 seconds and the values were averaged over this period after automatic removal of parts of inadequate signal quality.

Color Doppler Imaging

Flow velocities in the retrobulbar CRA were measured using CDI. The CDI examinations were performed using an ultrasound device (Vivid 7 Color Doppler Ultrasound; GE Vingmed Ultrasound, Høvik, Norway) using a 7.5 MHz array probe. The probe was placed on the closed upper eyelid after the application of contact jelly (methylcellulose 2%). To minimize the exertion of pressure on the globe, the examiner supported his hand on the patient's forehead. Peak systolic flow velocity (PSV) and end diastolic flow velocity (EDV) were determined as described previously.^{21,22} Resistive index was calculated as $\text{RI} = (\text{PSV} - \text{EDV})/\text{PSV}$.

Statistical Analysis

All variables were checked for normal distribution using the Kolmogoroff-Smirnov test. Effects of ranibizumab injection on hemodynamic parameters were assessed by repeated measures ANOVA using the absolute values. Post hoc analysis was performed using planned comparisons with Bonferroni correction for multiple comparisons. A one-way ANOVA was used to test whether the results were dependent on the number of re-treatments. A two-tailed $P < 0.05$ was considered as the level of significance. Results are given as mean \pm SD. Calculations were performed using the linear correlation analysis (Statistica Release 6.0; StatSoft, Tulsa, OK).

RESULTS

Three patients were lost for follow up and were not included in the statistical analysis. Baseline characteristics of the remaining 27 patients are presented in Table 1. Eleven patients were

TABLE 1. Patient Characteristics at Baseline

	Mean \pm SD
<i>N</i>	30*
Age, y	66.9 \pm 11.7
Sex (male/female)	16/14
Eye (right/left)	11/19
Systolic blood pressure, mmHg	146.9 \pm 23.6
Diastolic blood pressure, mmHg	74.1 \pm 14.4
Heart frequency, beats/min	78.0 \pm 12.7
Study Eye	
Intraocular pressure, mmHg	15.0 \pm 2.3
Retinal arterial diameter, μm	128.0 \pm 13.6
Retinal venous diameter, μm	153.8 \pm 22.2
Peak systolic velocity in the central retinal artery, cm/s	10.4 \pm 3.0
End diastolic velocity in the central retinal artery, cm/s	2.3 \pm 1.4
Resistive index in the central retinal artery, cm/s	0.78 \pm 0.10
Contralateral Eye	
Intraocular pressure, mmHg	15.5 \pm 2.4
Retinal arterial diameter, μm	123.2 \pm 10.6
Retinal venous diameter, μm	151.9 \pm 23.2
Peak systolic velocity in the central retinal artery, cm/s	10.2 \pm 2.5
End diastolic velocity in the central retinal artery, cm/s	2.4 \pm 1.2
Resistive index in the central retinal artery, cm/s	0.76 \pm 0.12

* Three lost to follow-up.

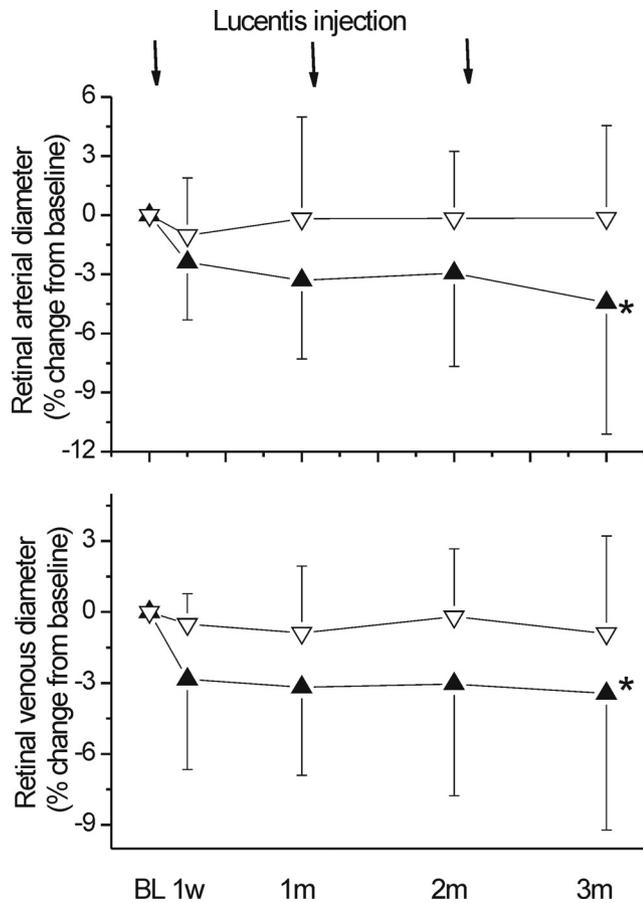


FIGURE 1. Retinal arterial (upper) and venous (lower) diameters in study eyes (solid up triangles) and in the contralateral eyes (open down triangles) over the treatment period of three months. Data are presented as percentage change from baseline. Error bars represent SDs. Asterisks indicate statistically significant influence of ranibizumab treatment on the retinal vessel diameter. BL, baseline; 1w, 1 week; 1m, 1 month; 2m, 2 months; 3m, 3 months.

re-treated after one month based on the criteria presented above. After two months, 14 patients were treated with ranibizumab. Accordingly, seven patients received one treatment, 15 patients received two treatments, and five patients received three treatments during the study period. The injections were well tolerated and no serious adverse events were observed. Neither systemic hemodynamic parameters nor IOP changed in response to ranibizumab treatment (data not shown).

In one patient, no RVA measurements of adequate quality could be obtained and accordingly, data of only 26 patients were included. Retinal vessel diameters over the treatment period are shown in Figure 1. A significant vasoconstriction in retinal veins ($P < 0.001$ versus baseline) and in retinal arteries ($P = 0.001$ versus baseline) of the affected eyes was seen. In the contralateral eyes, no changes in vessel diameters were seen (arteries: $P = 0.30$, veins: $P = 0.081$). The vasoconstrictor effect in retinal arteries ($P = 0.70$) and retinal veins ($P = 0.54$) was not dependent on the total number of treatments.

In 14 patients, a decrease in retinal arterial diameters of $>2\%$ was seen after three months. The maximum decrease in retinal arterial diameter that we observed in an individual was as high as 14%. In 10 patients, the change in retinal arterial diameter was between -2% and $+2\%$. In two patients, an increase in retinal arterial diameter of $>2\%$ was observed. In retinal veins a decrease in diameters of $>2\%$ was seen in 15 patients after three months. The same individual who showed

the most pronounced decrease in retinal arterial diameters also showed the most pronounced decrease in retinal venous diameter (15%). In nine patients, changes in retinal venous diameters were between -2% and 2% , whereas two patients showed a vasodilatation of $>2\%$.

In one patient, no adequate CDI measurements could be obtained. Hence, the presented data arise from 26 patients only. Data of CDI measurements as obtained in the CRA are presented in Figure 2. In response to ranibizumab treatment, a reduction in flow velocities in the CRA was observed over time (PSV: $P = 0.003$; EDV: $P = 0.003$). By contrast, RI in the study eye did not change after treatment with ranibizumab ($P = 0.76$). In the contralateral eyes no change in CRA blood velocities was seen (PSV: $P = 0.36$; EDV: $P = 0.91$; RI = 0.97). In the study eye, the decrease in CRA PSV ($P = 0.97$) and EDV ($P = 0.39$) was independent of the number of treatments.

In 10 patients, the decrease in PSV was $>10\%$ after three months, whereas in the other patients the change in PSV was between -10% and $+10\%$. For EDV, 16 patients showed a decrease of $>10\%$ after three months, whereas in the other patients change between -10% and $+10\%$ was observed after three months. Visual acuity over the treatment period increased from 43.4 ± 14.2 letters to 57.4 ± 11.7 letters after the three months' treatment period ($P < 0.001$). After three months, the percentage change in VA was not correlated with

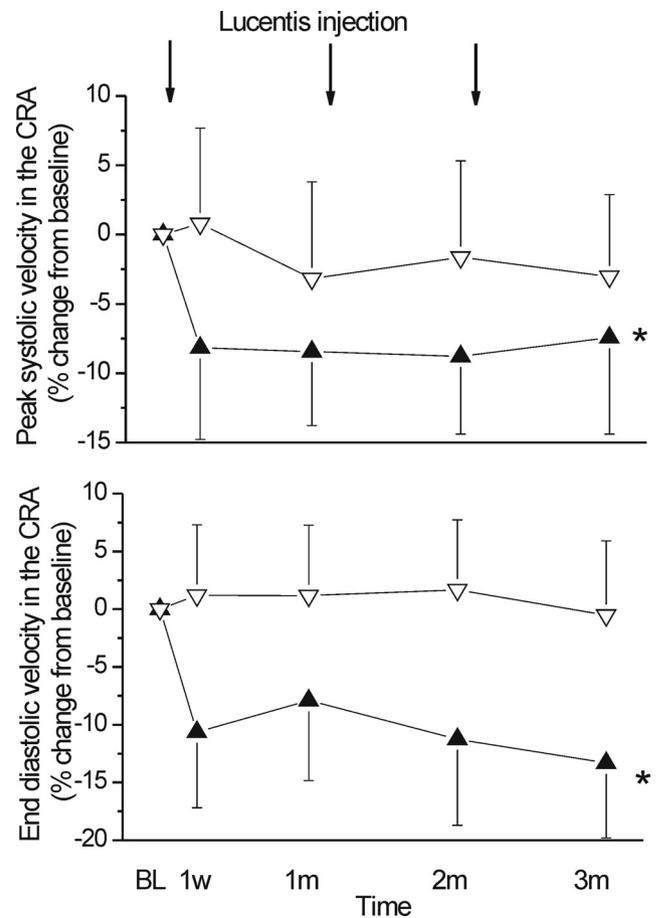


FIGURE 2. Color Doppler imaging measurements (peak systolic velocity [upper], end diastolic velocity [lower]) as obtained in the central retinal artery (CRA) in the study eyes (solid up triangles) and in the contralateral eyes (open down triangles) over the treatment period of three months. Data are presented as percentage change from baseline. Error bars represent SDs. Asterisks indicate statistically significant influence of ranibizumab treatment on the retinal flow velocities. BL, baseline; 1w, 1 week; 1m, 1 month; 2m, 2 months; 3m, 3 months.

the percentage change in retinal arterial diameter ($r = -0.16$), retinal venous diameter ($r = -0.25$), PSV in the CRA ($r = -0.16$), or EDV in the CRA ($r = -0.25$).

DISCUSSION

In the present study, we focused on the effects of ranibizumab treatment in patients with BRVO on ocular hemodynamic parameters. Vasoconstriction in retinal branch arteries and veins in non-affected quadrants was seen. In addition, we observed a reduction in blood velocities in the retrobulbar CRA in the affected eye after ranibizumab treatment. Both results indicate that ranibizumab treatment is associated with retinal vasoconstriction in patients with BRVO. This has already been reported for patients with AMD previously.^{23,24}

An additional aim of this study was to identify whether the retinal vessel response is a marker of treatment success in patients with BRVO. In a previous report, we have shown that the early vasoconstrictor response to ranibizumab treatment is a good indicator of the visual acuity outcome after laser photocoagulation in BRVO.¹⁵ This indicates that in the successfully treated eye the level of hypoxia is reduced, leading to retinal vessel vasoconstriction. In the present study, we tested this hypothesis by employing correlation analysis, compatible with the idea that hypoxia is the major trigger of VEGF in BRVO. In contrast to laser treatment, however, no correlation between the degree of vasoconstriction and the VA outcome was found after ranibizumab treatment. In addition, the degree of vasoconstriction was not dependent on the number of re-treatments. This is most likely related to the difference in the mechanisms underlying laser and anti-VEGF treatments in BRVO. Whereas the main aim of laser treatment is to reduce hypoxia,^{16,17} the main aim of anti-VEGF administration is to reduce edema formation. Vasoconstriction after ranibizumab may simply be caused by the reduction of retinal VEGF levels, thereby reducing vasodilator tone. A large number of studies has reported that VEGF is a potent vasodilator in many vascular beds including the retina, which exerts its action at least partially via a nitric oxide dependent mechanism.²⁵⁻²⁷

Could the retinal vasoconstrictor response after ranibizumab limit the clinical use of the drug in diseases like BRVO and central retinal vein occlusion? One may hypothesize that this vasoconstrictor response may further predispose for ischemia, which is a major cause of vision loss in these disorders.⁷ Indeed, several case reports have indicated that intravitreal anti-VEGF administration may be associated with severe retinal blood flow disturbances.^{28,29} In the present study, changes in retinal vessel diameters were small in most patients, although a decrease in retinal vessel diameters up to 14–15% was observed in one individual. This decrease was not associated with a loss in BCVA in this subject, although the estimated decrease in retinal blood flow was as much as 28–30%. In the present study, the number of included patients was small and the observation period short. Hence, it cannot be answered from our data whether the vasoconstrictor response seen here is indeed a risk factor for long-term loss of vision in BRVO patients after anti-VEGF treatment. On the other hand, several small-scale studies have shown that anti-VEGF treatment reduces macular edema and improves visual acuity in BRVO.³⁰⁻³³ Finally, this question can, however, only be answered in a multicenter clinical outcome trial investigating the long-term results of ranibizumab versus standard laser treatment.

In interpreting the results of the present study, a number of limitations need to be mentioned. Most importantly, no control group was studied in which the natural course of retinal vessel diameters after BRVO was observed. Including an untreated control group in the present trial nowadays seems impossible

due to ethical reasons. Unfortunately, the natural course of retinal vessel diameters after BRVO is unknown. Generally, vasodilatation may be expected in the natural course of a disease like BRVO due to hypoxia and VEGF release. Whether this, however, also occurs in patients with no angiographic or clinical signs of ischemia, as included in the present study, is unclear. The vasoconstrictor response to VEGF inhibition was, however, also seen in patients with neovascular AMD, showing an entirely different pathophysiology. This supports the hypothesis that ranibizumab treatment was responsible for vasoconstriction in the present study. In addition, neither the RVA nor CDA is capable of measuring retinal blood flow. Measurement of retinal vessel diameters may in principle be combined with bi-directional laser Doppler velocimetry to assess total retinal blood flow,³⁴ but such measurements are extremely difficult in patients with retinal vascular disease. In the future, bi-directional optical Doppler tomography may overcome this problem.³⁵ With CDI only blood velocities in the CRA are measured, but vessel diameters cannot be quantified because of the limited resolution of ultrasound devices. Interestingly, RI in the CRA did not change despite the reduction of flow velocities, but the validity of RI as a measure of distal vascular resistance in the retina has been questioned.³⁶

To conclude, in patients with macular edema secondary to BRVO, ranibizumab leads to retinal vasoconstriction, which is not related to the change in VA. Anti-VEGF offers promising alternatives to destructive treatments like focal laser coagulation in BRVO. Long-term studies are required to study whether this retinal vasoconstrictor response limits the success of this approach in retinal occlusive disease.

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