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Efficacy and safety of anti-VEGF therapy with intravitreal ranibizumab (LUCENTIS™) for naïve retinal vein occlusion: one-year follow-up

Alfredo Pece, MD, Vincenzo Isola, MD, Stefano Piermarocchi, MD, Giliola Calori, MD

Department of Ophthalmology, Melegnano Hospital (AP, VI) Milan, Italy; Department of Ophthalmology, University of Padua (SP), Italy; Statistics and Epidemiology Unit, San Raffaele University Hospital (G. Calori), Milan, Italy.

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Corresponding author:

Alfredo Pece, MD,

Department of Ophthalmology, Melegnano Hospital,

Via Pandina 1, 20077 Vizzolo Predabissi, Milan, Italy

Ph: +39 02 98052267; Fax: +39 02 2042262

e-mail: pece.retina@mclink.it

ABSTRACT

Purpose: To evaluate the efficacy and safety of intravitreal ranibizumab (Lucentis) in patients with treatment-naïve retinal vein occlusion (RVO).

Design: Prospective, consecutive, non-comparative, interventional case series.

Participants: Seventeen eyes of 17 consecutive patients with naïve RVO.

Methods: Consecutive patients were recruited and received, on demand, intravitreal 0.5 mg of ranibizumab; nine had central retinal vein occlusion (CRVO) and eight branch retinal vein occlusion (BRVO). Pre- and postoperative clinical evaluation included measurement of best corrected visual acuity (BCVA) for distance, and near vision (MNREAD time, reading fluency), contrast sensitivity, color fundus photography, fluorescein angiography, and optical coherence tomography (OCT). All subjects were followed for a minimum of 12 months.

Main outcome measures: Change in BCVA, contrast sensitivity, angiographic leakage, OCT central macular thickness (CMT), number of treatments.

Results: Patients with CRVO had mean pre-treatment BCVA of 20/240 (1.08 ± 0.25 logMAR) and final BCVA of 20/46 (0.36 ± 0.16 logMAR), with significant improvement at one year of follow-up ($p < 0.0001$). At 12 months mean BCVA improved 36.7 letters, with a gain of 6.4 lines, and OCT showed that the mean CMT was 271 μm , with a mean reduction of 360 μm ($p < 0.0001$) from baseline (mean 631 μm). Patients with BRVO had mean pre-treatment BCVA of 20/126 (0.80 ± 0.29 logMAR) and final BCVA of 20/50 (0.41 ± 0.23 logMAR) ($p < 0.0001$). The mean OCT CMT was 278 μm , with a mean reduction of 275 μm ($p < 0.0001$) from baseline (mean 553 μm). Contrast sensitivity, MNREAD time and reading fluency improved significantly in the treated eyes. No ocular or systemic side effects were observed. Eyes with CRVO received an average of 3 injections (range 2 to 4) and those with BRVO 3.6 (range 3 to 4).

Conclusions: Intravitreal ranibizumab for the management of naïve CRVO or BRVO can favorably modify the course of the occlusion, indicating that short- and long-term blockade of VEGF-A may restore the integrity of the inner blood-retinal barrier, reduce CMT, and significantly improve visual function, with a good safety profile. Further prospective long-term studies are warranted to confirm the efficacy, safety, and optimal treatment regimen for intravitreal ranibizumab.

Introduction

Branch and central retinal vein occlusions (RVO) are among the most common retinal vascular diseases, and are often associated with moderate to severe vision loss.¹ More than 90% of RVO occur in patients older than 50 years, but they are reported in all age groups.^{2,3} Central retinal vein occlusion (CRVO) results from thrombosis in the central retinal vein within the optic nerve at variable distances posterior to the lamina cribrosa, with fundus hemorrhage involving the entire retina with edema, dilated retinal vein and disc swelling.¹⁻⁴ Branch retinal vein occlusion (BRVO) occurs at more distal sites and is caused by focal occlusion of a retinal vein at an arterio-venous crossing-point where compression of the vein by the artery passing anteriorly produces turbulence and thrombosis with hemorrhage and edema that usually involve the superior or inferior temporal retinal vein.⁵⁻⁷

The exact pathogenesis of the occlusion is poorly understood but various local and systemic factors appear to play a role in the pathological closure of the retinal veins.⁸⁻¹³ The most common risk factors are the same as for cardiovascular disease, including systemic hypertension, atherosclerotic vascular changes, diabetes mellitus, and age over 65.^{3,8-11} Open-angle glaucoma is also considered a major risk factor and in recent years hyperhomocysteinemia and hypercoagulable risk factors have been increasingly implicated.^{12,13}

Visual acuity can be lost due to retinal ischemia or cystoid macular edema caused by capillary leakage, with endothelial cell damage combined with increased intracapillary pressure promoting exudation of extracellular proteins, intraretinal fluid, blood, and precipitation of lipids in the macula. The pathogenesis of macular edema is generally related to up-regulation of vascular endothelial growth factor A (VEGF-A) that may act on capillary hyperpermeability by increasing vesicular transport and/or lowering the content of tight-junction proteins among the endothelial cells.¹⁴⁻¹⁶ Therefore it seems rational to inhibit VEGF-A with the intent of normalizing the inner blood-retinal barrier, reducing vascular leakage and macular edema, and improving visual function.

Short-term clinical trials have shown the effectiveness and safety of intravitreal anti-VEGF-A therapy for treating CRVO. Validation of VEGF-A targeting for therapeutic intervention in CRVO and BRVO comes from clinical studies involving two different intravitreal anti-VEGF-A drugs: bevacizumab (Avastin, Genentech/Roche, Basel, Switzerland,) and pegaptanib sodium (Macugen, OSI-Eyetech Pharmaceuticals, New York, NY).¹⁸⁻²⁵ Ranibizumab (Lucentis, Genentech, Inc, South San Francisco, CA) is a FDA-approved anti-VEGF-A monoclonal antibody designed specifically to treat exudative age-related macular degeneration (AMD).²⁶ Two large clinical trials are currently in progress to investigate the efficacy and safety of ranibizumab injections in patients with macular edema secondary to CRVO (CRUISE) or BRVO (BRAVO).^{27,28} The purpose of the present study was to compare visual acuity, reading performance and contrast sensitivity in patients assigned to receive intravitreal injections of ranibizumab for non-ischemic CRVO or BRVO with macular edema.

Materials and Methods

We followed in a prospective open-label study 17 eyes of 17 consecutive patients with RVO who were treated with intravitreal injection of 0.5 mg of ranibizumab. The outcome of this study was to determine the efficacy and safety of ranibizumab in the treatment of macular edema associated with RVO by investigating the following variables:

(1) proportion of patients losing ≤ 15 letters or gaining > 15 letters as measured by using Early Treatment Diabetic Retinopathy Study (ETDRS) acuity charts and converted to logMAR (logarithm of the minimum angle of resolution) scale; (2) ETDRS vision determination compared to baseline, at 1 week, month 1, 2, 3 and at every three months for 1 year; (3) changing in reading acuity and contrast sensitivity (CS); (4) percentage of patients losing > 30 letters at month 1, 2, 3, 6, 9, and 12; (5) changing in central macular thickness (CMT) as measured by OCT at 1 week, and at

month 1, 2, 3, 6, 9, and 12 compared to baseline. For safety concern, local and systemic adverse effects were monitored throughout the study.

Subject Eligibility and Exclusion Criteria

To be eligible, the following inclusion criteria must be met: age ≥ 55 years; diagnosis of macular edema secondary to CRVO or BRVO at least 3 months from the time of the occlusive event; best corrected ETDRS visual acuity measurement from 20/50 to 20/400; baseline central foveal thickness 250 μm or greater using optical coherence tomography (OCT-3 Stratus; Carl Zeiss, Dublin, CA).

Exclusion criteria included ocular diseases other than CRVO and BRVO related macular edema such as age-related macular degeneration, diabetic retinopathy, uveitis, macular pucker, intraocular surgery within the past 3 months, dense cataract, glaucoma, evidence of neovascularization involving iris, retina or optic disc; brisk relative afferent pupillary defect predictive of non perfused CRVO; previous laser (grid laser or panretinal photocoagulation) within the past 3 months; anti-VEGF treatment within the past 3 months or intravitreal or periocular steroid administration in the study eye that could interfere with the treatment result; evidence of external ocular infection including blepharitis, conjunctivitis, or chalazion.

Patients were scheduled to be evaluated with retinal biomicroscopy, color fundus photography, fluorescein angiography, and OCT at baseline, at 1 week and 1, 2, 3, 6, 9 and 12 months.

The patients received an initial injection on day 0 and were then retreated as needed (*pro re nata* (PRN)). All patients were also examined with anterior and posterior slit-lamp biomicroscopy, Goldmann applanation tonometry, the day after each injection and were asked if they had decreased vision, eye pain, or any new symptoms.

After obtaining written informed consent, off-label anti-VEGF therapy was administered in the operating room observing a sterile protocol for intravitreal injection that included the use of 5%

povidone-iodine solution, topical anesthesia, eyelid-speculum application, intravitreal injection of 0.5 mg of ranibizumab via pars plana in the infero-temporal quadrant at 4 mm from the limbus in the phakic eye and at 3.5 mm in the pseudophakic eye followed by postoperative topical antibiotic eye-drops medication. Patients were given topical netilmicin + dexamethasone four times daily for two weeks after injection.

Retreatment criteria

Repeated intravitreal injection was performed on the basis of persistence or increase in central macular edema as determined by OCT (CMT 250 μ m or greater) or decreased vision when compared to last visit; patients who were eligible for re-treatment were evaluated the day after intravitreal re-injection, and then as the protocol.

Statistical analysis

Data are shown as number (%) for categorical variables or as mean and standard deviation (SD) for continuous variables. To investigate the trend of visual function with time, one way analysis of variance (ANOVA) for repeated measures was used. When it turned out to be statistically significant the comparison of each time point with the baseline was tested, adjusting by Bonferroni's procedure. In order to investigate the association of changes among BCVA scores (distance and near vision), contrast sensitivity and CMT, a correlation analysis was run and Pearson correlation coefficient was calculated. The correlation between the maximum peak of BCVA and the CMT at the same time was also investigated. The p-value has been set at 0.05. Statistical analyses were performed by SAS v8 software (SAS Institute Inc, Cary, NC-USA).

Procedure

Testing were conducted at the Author's Institution by one vision examiner who performed all visual acuity and contrast sensitivity testing of participants. Written informed consent was obtained from all patients before the beginning of the examination session, and our study complied with the tenets of Helsinki Declaration.

Distance Visual Acuity Testing

Each patient's best corrected VA was tested with the ETDRS charts (ETDRS Illuminator Cabinets,TM Precision Vision, La Salle, IL, USA). Initially, each patient was asked to identify 10 large, individual ETDRS letters that were held by the vision examiner at a distance of 1.5 m. The distance VA of the study eye was tested at the standard distance of 4 m, using 1 of the 3 ETDRS charts. Patients were asked to identify the first 3 letters on each line. If the patient incorrectly identified 1 or more of the letters, he or she was asked to identify the remaining letters on that line. VA was recorded as the Snellen equivalent, logMAR value, and letter score of the last line on which the patients identified 3 or more letters correctly.

Near Visual Acuity Testing

The MNREAD acuity charts (Lighthouse Low Vision Products, Long Island City, NY, USA) were used to measure reading vision. Reading acuity was determined by the smallest print size at which the patient can read an entire sentence without making significant errors. For this study, reading acuity was measured at 25-cm distance with the patient wearing an additional +4.00 DS over his distance correction and was recorded in logMAR units using the formula provided by the manufacturer: $\text{acuity} = 1.4 - (\text{sentences} \times 0.1) + (\text{errors} \times 0.01)$, in which sentences are the number of sentences read correctly and errors are the number of words read incorrectly. The calculated value was adjusted for the viewing distance by adding to the measured acuity a +0.204 logMAR correction.

Contrast Sensitivity Testing

Contrast sensitivity of each patient's affected eye was measured using the commercially available Pelli-Robson contrast sensitivity chart (Clement Clark Inc, Columbus, Ohio, USA). Test distance was 1 meter, and the CS chart was front-illuminated uniformly to a luminance of 64 cd/m² or more. Patients were asked to make a single attempt to identify each letter on the chart, starting with discriminations of high contrast letters in the upper left corner of the chart and reading across each line. Patients were asked to guess even when they indicated that the letters were invisible. CS was

recorded by the log contrast sensitivity value ($\log_{10} 1/\text{contrast}$ of letters at the threshold of visibility) of the last triplet on which the subject identified at least 2 of the 3 letters correctly, and also by the total number of letters identified by the patients.

Photographic Documentation

Color Fundus Photography and Fluorescein Angiography

The clinical appearance of RVO was documented with color fundus photography and retinal angiography (FA) for all patients at baseline and again at 1 month, 3 months, 6-9 months and 1 year to evaluate any changes in the aspect of the retina treated with intravitreal injection of ranibizumab. Color photography of the disc and macula of each affected eye were performed with the Topcon ImageNet Digital Imaging System (Paramus, NJ). Intravenous fluorescein angiography was performed with a confocal scanning laser ophthalmoscope (HRA, Heidelberg Retinal Angiograph, Heidelberg Engineering, Carlsbad, CA). Single angiograms were obtained in the early, middle and late phase between 2 and 5 minutes after injection to document fluorescein leakage from arteries, veins, capillary vessel walls and optic disc as well as pooling of dye in the center of the macula. Angiography was also the gold standard to distinct about retinal capillary perfusion status, and whether the vascular occlusion was ischemic when 10 or more disc areas of hypoperfusion were detectable.

Optical Coherence Tomography

Third-generation OCT examination (Stratus Tomographer, Model 3000, Carl Zeiss Ophthalmic System Inc, Humphrey Division, Dublin, CA) was performed in all patients to measure the central macular thickness (CMT) at baseline and at each follow-up visit on the first week, and then at month 1, 2, 3, 6, 9, 12 after treatment. Patients who needed to be reinjected were examined again with OCT following the same time-point described above. The OCT map was created from six consecutive linear 6 mm scans

oriented at intervals of 30° and centered on the foveal region. The fundus image generated by OCT machine during the procedure was used to center the scan at the fovea for each examination.

Results

Seventeen eyes of 17 consecutive patients were included in this cohort study. Nine patients had a CRVO and 8 patients had a BRVO. All patients completed the 1-year follow-up. Demographic and clinical characteristics, including age, gender, duration of occlusion, and associated medical conditions are displayed in Table 1.

Central Retinal Vein Occlusion (CRVO)

Distance Visual Acuity

Patients with CRVO had a mean BCVA before treatment of 20/240 (1.09 ± 0.25 logMAR) and a final BCVA of 20/46 (0.36 ± 0.16 logMAR) that was significantly improved at the end of follow-up ($p < .0001$). The mean BCVA changes from baseline in logMAR unit and ETRDS letters scores are summarized in Figure 1 and Table 2, respectively. VA improvement was highly significant at 1 week, and 1, 2 months after the first injection. At 3, 6 and 9 months postoperatively, the mean values of BCVA in logMAR and ETDRS letter scores declined with a regression of the increase in mean logMAR BCVA and ETDRS letters. Therefore, the most important finding of this analysis was a statistical significant improvement in logMAR BCVA and ETDRS letter scores 1 week after each ranibizumab injection at 3, 6, and 9 months of follow-up. At 12 months, eyes showed a maintaining of BCVA improvement with a mean of 36.7 letters and a gain of 6.4 lines. The mean BCVA compared to baseline, improved more than 3

lines for 90% (8 eyes), remained stable for 10% (1 eye), and did not worsen in any eye. Eyes received an average number of 3 intravitreal injections (range: 2 to 4).

Near Visual Acuity

Patients with CRVO had a mean in MNREAD time $\pm$ SD (seconds) and reading fluency $\pm$ SD (words/minute: wpm) before treatment of 8.3 ± 8.5 seconds and 75.3 ± 43.8 wpm with a final mean in MNREAD time of 3.5 ± 0.4 seconds ($p < .006$) and in reading fluency of 173.2 ± 20.43 wpm ($p < .0002$) that were significantly improved at the end of follow-up. The mean change in MNREAD time and reading fluency from baseline are summarized in Figure 2 and Table 3. After 1 week, the mean in MNREAD time $\pm$ SD improved significantly to 3.8 ± 0.9 seconds ($p < .0001$) and to 150.1 ± 29.51 wpm ($p < .0001$), whereas no significant ($p > .05$) change was observed at month 1, 2 and 3. Therefore, the analysis indicated that a statistically significant improvement in MNREAD time and reading fluency was recorded 1 week after each ranibizumab injection at 3, 6, and 9 months of follow-up. At 12 months, the efficacy of treatment over near visual acuity was still statistically significant.

Contrast Sensitivity

Patients with CRVO had a mean log contrast sensitivity (CS) value $\pm$ SD and number of Pelli-Robson letters $\pm$ SD before treatment of 0.55 ± 0.28 and 14.3 ± 8 with a final mean log CS of 1.23 ± 0.14 ($p < .0002$) and 28.3 ± 2.95 letters ($p < .0001$) that were significantly improved at the end of follow-up. Contrast sensitivity results are given in Figure 3 for log CS and in Table 4 for number of Pelli-Robson letters correctly identified. After 1 week, the mean log CS $\pm$ SD significantly improved to 1.01 ± 0.27 log ($p < .0001$) and to 23.1 ± 5.41 letters ($p < .0001$). The efficacy of the first injection

was reported between month 1 and 2 of follow-up. Three and six months postoperatively, some regression of the increase in mean log CS and Pelli-Robson letter score was recorded. Therefore, the analysis indicated that a statistical significant improvement in mean log CS value and number of Pelli-Robson letters was recorded 1 week after each ranibizumab injection at 3, 6 months of follow-up. The result of the line graph indicated that the efficacy of treatment was maintained statistically ($p < .0001$) significant between month 6+1 week and month 12 for log CS and number of Pelli-Robson letters.

Optical Coherence Tomography (OCT)

All of the 9 eyes had a significant decrease in the mean of CMT compared to baseline. Changes in CMT are summarized in Figure 4 and Table 5. Statistically significant reduction in CMT was evident 1 week after injection thus eliminating 52.9% of macular edema after the first injection, 60.4% after the second injection (3 month+1wk), 60.5% after the third injection (6 month+1wk), 61.1% after the fourth injection (9 month+1wk). However, the correlations between the CMT changes and the logMAR BCVA were not statistically significant (Pearson correlation: $r = -0.29$; $p > 0.45$). The improvements in BCVA, reading fluency, contrast sensitivity, and CMT recorded until two months after each injection were gradually decreased overtime during the following 2 months after each treatment owing to recurrent macular edema at month 3, 6 and 9.

Branch Retinal Vein Occlusion (BRVO)

Distance Visual Acuity

Patients with BRVO had a mean BCVA before treatment of 20/126 (0.80 ± 0.29)

logMAR) and a final BCVA of 20/50 (0.41 ± 0.23 logMAR) that was significantly better than the acuity at baseline ($p < .0001$). The mean BCVA changes from baseline in logMAR unit are summarized in Figure 1 and ETDRS letters scores are illustrated in Table 6. After 1 week, mean BCVA $\pm$ SD improved to 0.54 ± 0.20 logMAR ($p < .0001$) and to 58.5 ± 10.9 ETDRS letters ($p < .0001$). After 1, 2 and 3 months, some regression of the increase in mean BCVA and ETDRS letters was recorded. The most important findings we observed was a statistically significant improvement in logMAR BCVA and ETDRS letter score 1 week after each injection at month 6, and 9 of follow-up, and this gain was maintained at 12 months. Moreover, after 1-year of treatment the mean BCVA significantly improved of 25.3 ETDRS letters. Comparisons between month 12 and baseline for mean BCVA were considered indicative for improvement of more than 3 lines for 63% (5 eyes), unchanged for 37% (3), and worsened for any eye. Eyes received a mean number of 3.6 injections of ranibizumab (range: 3 to 4).

Near Visual Acuity

Patients with BRVO had a mean in MNREAD time $\pm$ SD (seconds) and reading fluency $\pm$ SD (words/minute: wpm) before treatment of 7.7 ± 3.01 seconds and 82.25 ± 17.27 wpm with a final mean in MNREAD time of 4 ± 0.8 seconds ($p < .006$) and in reading fluency of 154.2 ± 34.12 wpm ($p < .0002$) that were significantly improved at the end of follow-up. The mean changes in MNREAD time and reading fluency from baseline are summarized in Figure 2 and Table 7. After 1 week, the mean in MNREAD time $\pm$ SD and reading fluency $\pm$ SD was statistically significant improved to 5.4 ± 1.7 seconds ($p < .0001$) and to 120.4 ± 37.8 wpm ($p < .0001$). After the initial improvement, the results indicated some regression of the increase in mean MNREAD time and reading fluency between month 1 and month 3. Therefore, the most important

finding of this analysis was a statistical significant improvement in near visual acuity 1 week after each ranibizumab injection at 3, 6, and 9 months of follow-up. This gain was maintained at 12 months, with a highly significant improvement of MNREAD time and reading fluency.

Contrast Sensitivity

Patients with BRVO had a mean log contrast sensitivity (CS) value $\pm$ SD and number of letters $\pm$ SD before treatment of 0.86 ± 0.34 and 19.8 ± 9.39 with a final mean log CS of 1.24 ± 0.10 ($p < .0002$) and 27.9 ± 2.3 letters ($p < .0001$) that were significantly improved at the end of follow-up. Contrast sensitivity results are given in the graph illustrated in Figure 3 for log CS and in Table 8 for number of Pelli-Robson letters correctly identified. After 4 intravitreal injections occurred at time 0, month 3, month 6, month 9, the eyes showed some benefit in the mean of log CS value and number of Pelli-Robson letters that was highly significant at 9 months+1 week, whereas no significant ($p > .05$) change was found between baseline and month 9.

Optical Coherence Tomography (OCT)

All of the 8 eyes had a significant reduction in the mean of CMT after every single injection compared to baseline. Changes in CMT are summarized in Figure 4 and percentage of eliminated macular edema were shown in Table 9. Statistically significant reduction in CMT was observed 1 week after the first injection and subsequent injections compared to pre-injection values thus eliminating 42.5% of macular edema after the first injection, 50.7% after the second injection (3 month+1 wk), 54.1% after the third injection (6 month+1 wk), 62.7% after the fourth injection (9 month+1 wk). Highly significant reductions of CMT when compared with baseline at all time points were recorded. However, the correlations between the CMT changes and the logMAR

BCVA were not statistically significant (Pearson correlation: $r = -0.41$; $p > .66$). The improvements in BCVA, reading fluency, contrast sensitivity, and CMT recorded until two months after each injection were gradually decreased overtime during the following 2 months after each treatment owing to recurrent macular edema at month 3, 6 and 9.

Color Fundus Photography and Fluorescein Angiography

At baseline CRVO showed extensive haemorrhages in all four quadrants, macular thickening, very few or no cotton wool spots, dilated and tortuous veins, and optic disc edema. BRVO presented the same aspects but only in one quadrant with apex of hemorrhage at an arteriovenous crossing. In all eyes a gradual decrease of intraretinal blood and optic disc swelling was observed 3 months after the first ranibizumab injection, with a complete disappearance at 6-9 months after the second and third intravitreally ranibizumab injection respectively, for both CRVO (Figure 5) and BRVO (Figure 6). Consistent with a decrease in CMT as seen by OCT, fluorescein angiography showed a reduction of leakage with re-establishment in the inner blood-retinal barrier at 1 week, month 1 and 2 after the first injection, and at every three monthly + 1 week after retreatment. However, a recurrence of leakage at month 3, 6, and 9 after treatment was observed in all patients.

Safety Reporting

After 1-year of follow-up, no serious adverse ocular and systemic side-effect was reported from any of the patients in the study during the entire period of treatment; there were no IOP elevation, inflammatory reaction, endophthalmitis, retinal detachment, retinal tear, vitreous hemorrhage, traumatic cataract, cardiovascular or cerebrovascular

thromboembolic events. No patient developed neovascularization involving the iris, retina and optic disc. The most common side effects were a subconjunctival hemorrhage that was observed in 6 eyes, and floaters in 3.

Discussion

The management of macular edema due to RVO has been largely dependent on the results of two large randomized collaborative prospective clinical trials by CRVO and BRVO study groups.^{29,30} The CRVO Study²⁹ failed to show any benefit from macular grid laser for patients with CRVO. Although there was a significant reduction in the severity of macular edema in treated eyes compared to controls there was no visual acuity benefit, although a trend in favor of treatment was observed in younger patients. In contrast, laser treatment is effective for BRVO. The BRVO Study³⁰ showed that laser photocoagulation improved visual acuity in patients whose vision was 20/40 or worse because of macular edema; however, patients with vision worse than 20/200 did not do significantly better than with observation alone.

Some surgical procedures are also being tested: radial optic neurotomy and laser-induced chorioretinal anastomosis have been studied for CRVO.^{31,32} Currently, there are no randomized clinical investigations that show these treatment modalities reproducibly and reliably improve BCVA.³³

Other promising approaches include off-label intravitreal injection of triamcinolone acetonide (IVTA). Small case series and presentations on its use have increased over the last eight years. An analysis of the literature showed that almost all patients had anatomical improvements, and many gained visual acuity.³⁴⁻³⁶ This strategy seems effective in the short term, but there is the risk of adverse side effects such as the development of lens opacities and ocular hypertension.³⁷ Recently have been published

the results of the SCORE study (the Standard care versus corticosteroid for retinal vein occlusion). In this multicenter, randomized trial, 271 pt with central vein occlusion and macular edema have been treated with IVTA or only observed. IVTA was superior to observation and the 1-mg dose had a better safety profile.³⁸

The SCORE study, report 6, also investigated 411 pt with branch retinal vein occlusion and macular edema, treated with IVTA vs standard care. There was no difference in VA at 12 months in the two groups and therefore, considering also the high negative side effects in IVTA group, grid laser photocoagulation should remain the standard therapy in BRVO.³⁹

Therapies for CRVO and BRVO are still limited, but several new approaches have been described. There is increasing interest in intravitreally-injected anti-VEGF drugs for macular edema due to RVO. In clinical practice, there are now three commercially available VEGF antagonists: pegaptanib sodium (Macugen, OSI/Eyetech, and Pfizer), bevacizumab (Avastin, Genentech), and ranibizumab (Lucentis, Genentech). These are used on an off-label basis, however, and their long-term efficacy and safety are still not known.

Pegaptanib sodium is a modified fragment of ribonucleic acid that inactivates VEGF₁₆₅ and is FDA-approved for the treatment of exudative AMD.⁴⁰ A recent phase II randomized, double-masked, multicenter trial evaluated the role of pegaptanib in CRVO patients.²⁵ Results were encouraging for the efficacy and safety of intravitreal injections of pegaptanib for selective inhibition of VEGF₁₆₅ in eyes with recent vision loss due to macular edema secondary to CRVO. Preliminary comparisons of Macugen doses of 0.3 and 1.0 mg as an intravitreal injection every six weeks or sham injections every six weeks for 30 weeks have shown that RVO eyes receiving Macugen gained a mean of ten ETDRS letters as compared to a mean loss of two letters in the eyes receiving sham injections.

Bevacizumab is a full-length, humanized monoclonal antibody directed against all biological isoforms of VEGF. Treatment of CRVO and BRVO with intravitreal bevacizumab achieved significant reductions in vein diameter, tortuosity, optic disc edema, and macular thickening, with some gain in vision. Iturralde et al. ran a small, prospective, non-comparative trial of 16 eyes with CRVO and found a good response to 0.05 mL of intravitreal bevacizumab, with BCVA improvement and decrease in central foveal thickness.¹⁸

The drug has also shown promising early results and an excellent safety profile in the treatment of macular edema secondary to BRVO. Rebena et al. observed a positive biologic effect on macular edema in 27 eyes with BRVO that received 0.05 mL intravitreal bevacizumab injections. At three months, 44% of these eyes showed halving of the visual angle from baseline, and after a mean of 5.3 months there was a moderate correlation between decrease in retinal thickness and improvement in visual acuity.²⁰ In the IbeVO study, Costa et al. examined the effect of 0.08 mL of intravitreal bevacizumab at 12-week intervals in five eyes with CRVO and two with hemi-CRVO: there was a reduction in CMT, with short-term visual acuity stabilization or improvement of three or more ETDRS lines.¹⁹

Ranibizumab is a recombinant, humanized, monoclonal antibody antigen-binding fragment (Fab) that binds and neutralizes all the biologically active forms of VEGF.²⁶ Campochiaro et al. investigated the short-term effects of ranibizumab in eyes with CRVO and BRVO and found that monthly injections of 0.5 mg tended to cause more rapid decreases in central retinal thickening that lasted longer with three-monthly injections. At the final examination, OCT indicated that the excess retinal thickening was reduced by approximately 90% in all eyes.⁴¹ However, the lack of long-term outcomes did not allow any firm final conclusion on the routine use of ranibizumab for RVO. Pieramici et al. documented visual and anatomical success in ten patients with

perfused CRVO treated with ranibizumab monthly for three months, then quarterly as needed. However, the benefit may have statistical significance but only limited clinical impact because improvements in BCVA and OCT-CMT appeared greatest during the initial monthly injection period (0-3 months) and were lost -- with the recurrence of macular edema -- in between ranibizumab injections during the quarterly treatments (3-9 months).⁴²

Spaide et al. reported that intravitreal ranibizumab was effective in 16 eyes with non-naïve CRVO, using a loading phase with injections at baseline then at months 1 and 2, followed by monthly clinical examinations to check whether re-treatment was necessary on the basis of persistent macular edema or new retinal hemorrhages. This study evaluated the effect of ranibizumab in eyes that had already been treated with intravitreal triamcinolone (five eyes) and bevacizumab (11 eyes); only four CRVO patients were naïve to intravitreal ranibizumab. All eyes gained in VA as a result of additional injections over one year of follow-up.⁴³

Our prospective study found that after one year intravitreal ranibizumab for macular edema secondary to CRVO was associated with significant improvement in BCVA for 90% of patients, who gained more than three ETDRS lines from baseline ($p < 0.0001$). All patients showed an immediate response to these injections, with a significant reduction of CMT and an increase in acuity. OCT indicated a gradual decrease in intraretinal fluid and macular cysts. However, the reduction of cystoid edema was not statistically correlated with the change in distance, near vision, or contrast sensitivity. The BCVA for distance vision, reading ability, and contrast sensitivity seemed to recover transiently in all eyes, especially seven days after intravitreal ranibizumab, and visual benefits were observed during the first two months. This seems to be the interval at which treated individuals report the greatest acuity benefits. However, OCT reveals re-accumulation of macular fluid and a recurrence of edema after the initial

improvement in vision. This explains the decrease in VA that patients reported at 3, 6, and 9 months and is considered indicative of the loss of efficacy of the drug, that appears to be unable to maintain high levels of visual performance.

The recurrence of edema might be an indication that the disease is still active and treatment could be needed more often to counter this chronic vascular disorder. In one case, after the initial resolution of edema, there was a more pronounced increase than at the initial presentation. This rebound effect is still not completely clear, and Matsumoto et al. suggested VEGF receptors might be upregulated as a result of the inhibition of the VEGF-A pathway.⁴⁴ The mechanism inducing the gain in visual function in the early stage of ranibizumab treatment is also not entirely clear but we can speculate that changes in ocular circulation, re-establishment of normal foveal anatomy, and restoration of the inner blood-retinal barrier might be involved in the improvements in central vision.

In our series of eyes with BRVO intravitreal ranibizumab showed anatomic and functional effectiveness on macular edema, resulting in significant increases in BCVA, contrast sensitivity and reading ability, with a transient reduction of CMT. There was a significant long-term effect on CMT with a 48.5% elimination of macular edema and an improvement of more than three lines of BCVA in 63% of treated eyes at one year of follow-up. We did not use a loading phase regimen - monthly injections for three months – and considered both functional and anatomic criteria in order to guide treatment and re-injection decisions. This resulted in a smaller number of ranibizumab intravitreal injections in an attempt to maximize the benefit of visual gain and minimize the re-treatment rate. The mean number of injections from baseline was 3 for CRVO and 3.6 for BRVO. Pieramici et al. reported a mean of 4.5 injections through a nine-month follow-up and Spaide et al. a mean of 8.5 in a one-year prospective study.^{42,43} This is considerably more than the injections we gave in approximately the same

follow-up in our study. However, despite this difference, a similar gain of about three lines of VA, with significant elimination of macular edema, can still be obtained. It can therefore be reasonably assumed that more frequent injections are not necessarily associated with more functional and anatomic benefit than the PRN procedure.

A less-frequent-dose protocol in which ranibizumab was injected monthly for three months then quarterly for the treatment of neovascular AMD was employed in the PIER study (age-related choroidal neovascularization with or without classic CNV secondary to age-related macular degeneration) and provided VA benefit at 12 months.⁴⁵ However, the two diseases are completely different in their pathogenesis and in visual and clinical outcomes so it is impossible to draw any firm conclusions.

Our results suggest that multiple intravitreal injections of ranibizumab against VEGF-A can result in early recovery of the inner blood-retinal barrier with later stabilization and remodeling of retinal microvessels after retinal venous obstruction. Unlike pegaptanib, ranibizumab binds to and neutralizes the biological activity of all isoforms of VEGF-A proteins and their active metabolic products. However, whether selective VEGF₁₆₅ blockade with pegaptanib rather than pan-VEGF inhibition with bevacizumab or ranibizumab is appropriate in RVO patients remains to be established. The finding that short- and long-term blockade of VEGF-A action has no important intraocular adverse effects may argue against it being involved in maintaining endothelial cell permeability and the circulatory changes due to CRVO.

Retinal thickening and visual acuity at 3, 6, 9 and 12 months provided information on the duration of effect. The cumulative beneficial effect resulting from multiple doses was achieved over time. Preliminary data on 17 patients in this study suggest that visual function may improve with time. These encouraging anatomic and visual benefits may be observed not only in eyes with early-onset RVO but also in those with advanced occlusion and chronic edema, as reported by Campochiaro et al. Mean CMT

showed a significant reduction after every three-monthly injection in all 17 eyes. Given this information and clinical experience with off-label bevacizumab for CRVO and BRVO, our impression is that pan-VEGF inhibition with ranibizumab might last slightly longer than with bevacizumab. Besides, even if bevacizumab lowers the intraocular concentration of VEGF, other inflammatory cytokines and growth factors might be important in the recurrence of intraretinal fluid and macular edema.⁴⁶

Furthermore, ranibizumab has potentially better retinal penetration because of its smaller molecular size and higher binding affinity for VEGF-A aminoacid sequences than bevacizumab.

Then long-term care of venous thrombosis becomes an important issue. Perhaps as many as 30% to 60% of all RVO patients will require therapy for longer than a year and for some, indefinitely. With the likelihood of protracted treatment, we need to worry about the possible negative effects of pan-VEGF inhibition on the neuroretina. In answer to this question, it is worth recalling that pan-VEGF inhibition with ranibizumab every three months for a year did not cause detectable neuroretinal toxicity.

In conclusion, intravitreal injection of ranibizumab appears safe and may offer a new therapeutic opportunity for patients with RVO and macular edema, with a significant impact on visual function that needs to be investigated in the long term. These results must be interpreted cautiously because of the small number of eyes in this study, the absence of a control group, and the short follow-up. More conclusive evidence on the utility of intravitreal ranibizumab, also in comparison with other molecules, in the management of RVO will be forthcoming from current randomized, prospective, controlled, multicenter clinical trials.

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FIGURE LEGENDS

Figure 1. Mean change in LogMAR visual acuity from baseline in eyes treated with ranibizumab for central retinal vein occlusion(up) and branch retinal vein occlusion (bottom).

Figure 2. Mean change in reading fluency (wpm) from baseline in eyes treated with ranibizumab for central retinal vein occlusion (up) and branch retinal vein occlusion (bottom).

Figure 3. Mean change in log contrast sensitivity from baseline in eyes treated with ranibizumab for central retinal vein occlusion (up) and branch retinal vein occlusion (bottom).

Figure 4. Mean change in central macular thickness from baseline in eyes treated with ranibizumab for central retinal vein occlusion (up) and branch retinal vein occlusion (bottom).

Figure 5. Color fundus photography (**A**), late-phase fluorescein angiogram (**B**), and optical coherence tomography (OCT) scan (**C**) of a 76-year old woman with central retinal vein occlusion at baseline. Six months after the first intravitreal injection of 0.5 mg of ranibizumab, infrared fundus photography (**D**) and late-phase fluorescein angiogram (**E**) showed marked decreases in intraretinal bleeding, optic disc swelling and vascular leakage. The cross-sectional OCT image (**F**) of center-point retinal thickness indicated that the cystic spaces had resolved, with minimal intraretinal fluid. The patient's visual acuity improved from 20/200 to 20/50. At month 9 of follow-up infrared fundus photography (**G**) showed some intraretinal hemorrhagic dots, and the late-phase fluorescein angiogram (**H**) a decrease in fluorescein leakage from capillary microvessels throughout the macula. The OCT scan (**I**) showed less intraretinal fluid, with slight subfoveal neurosensory retinal detachment. Visual acuity was 20/64. The patient received a second intravitreal injection of ranibizumab. Color fundus photography (**J**), late-phase fluorescein angiogram (**K**) and OCT (**L**) one year after treatment showed restoration of foveal anatomy with normal macular thickness. Visual acuity improved to 20/20.

Figure 6. Color fundus photography (**A**), late-phase fluorescein angiogram (**B**) and optical coherence tomography (OCT) scan (**C**) of a 69-year old woman with right superotemporal branch retinal vein occlusion at baseline. One month after the first intravitreal injection of 0.5 mg of ranibizumab, infrared fundus photography (**D**) and the late-phase fluorescein angiogram (**E**) showed a decrease in intraretinal hemorrhages and vascular leakage along the distribution of the branch vein. The OCT image (**F**) of center-point retinal thickness indicated that the cystic spaces had resolved and the patient's visual acuity improved from 20/200 to 20/40. Infrared fundus photography (**G**), late-phase fluorescein angiogram (**H**) and OCT (**I**) three months after the injection showed recurrent macular edema with intraretinal cysts and fluid accumulation. The patient was given a second intravitreal injection of ranibizumab. At month 6, infrared fundus photography (**J**) showed no intraretinal blood and the late-phase fluorescein angiogram (**K**) indicated a reduction in fluorescein leakage. An OCT scan (**L**) showed partial resolution of the intraretinal fluid with recovery of the foveal contour; the macular cysts had disappeared almost completely. Visual acuity improved from 20/100 to 20/32. At month 9, infrared fundus photography (**M**) showed cystic macular changes and the late-phase fluorescein angiogram (**N**) indicated macular leakage with pooling of dye for persistent cystoid edema, confirmed by OCT (**O**). The patient received a third intravitreal injection of ranibizumab. At one year, color fundus photography (**P**) showed residual hemorrhages with small cotton wool spots; the late-phase fluorescein angiogram (**Q**) showed no leakage. An OCT scan (**R**) indicated restoration of a foveal profile with scant intraretinal fluid. Visual acuity improved from 20/80 to 20/25.

Table 1. Clinical Evaluation of Patients at Baseline

	CRVO	BRVO
N° of patients	9	8
Age in years (mean $\pm$ SD)	68.7 $\pm$ 7.5	66.5 $\pm$ 3.3
Gender (Male/Female)	3/6	4/4
Duration of occlusion (months)	3	3
Associated Medical Conditions		
Hypertension	6	3
Smoking history	5	4
Hypercholesterolemia	5	3
Hyperlipidemia	6	3
Diabetes	3	0
Glaucoma	1	0
Initial Snellen BCVA		
(logMAR $\pm$ SD)	20/240 (1.09 $\pm$ 0.25)	20/126 (0.80 $\pm$ 0.29)
Initial Reading Fluency		
wpm ($\pm$ SD)	75.3 ($\pm$ 43.08)	82.25 ($\pm$ 17.3)
Contrast sensitivity		
Log Unit ($\pm$ SD)	0.55 ($\pm$ 0.67)	0.86 ($\pm$ 0.26)
logMAR = logarithm of minimum angle of resolution		
wpm = word/per/minutes		
SD = standard deviation		

Table 2. Mean change in ETDRS letter score from baseline for Central Retinal Vein Occlusion

Time	Mean	s.d.
basal	29.9	13.2
1 week	61.6*	10.3
1 month	58*	7.6
2 month	47*	12.8
3 month	29.7	9.9
3 month+1wk	56.7*	5.0
6 month	39.4	6.8
6 month+1wk	67.9*	9.1
9 month	36.4	7.9
9 month+1 wk	66.8*	10.4
12 month	66.6*	7.4

$F_{9,63}=6.86$; $p<0.001$
* $p<0.005$ vs basal (Bonferroni)

Table 3. Mean change in reading time from baseline for Central Retinal Vein Occlusion

Time	Mean	s.d.
basal	8.3	8.5
1 week	3.8*	0.9
1 month	5.4	0.4
2 month	6.1	0.7
3 month	7.5	7.2
3 month+1wk	3.6*	0.9
6 month	6.3	8.2
6 month+1wk	3.7*	0.3
9 month	5.2	0.9
9 month+1 wk	3.6*	0.6
12 month	3.5*	0.4

$F_{9,72}=3.04$; $p=0.07$

* $p<0.005$ vs basal (Bonferroni)

Table 4. Mean change in number of letter on contrast sensitivity from baseline for Central Retinal Vein Occlusion

Time	Mean	s.d.
basal	11.33	8.00
1 week	23.11*	5.42
1 month	24.56*	3.81
2 month	23*	5.30
3 month	12.00	5.15
3 month+1wk	24.33*	3.16
6 month	12.33	4.03
6 month+1wk	26.89*	3.26
9 month	22.89*	5.67
9 month+1 wk	27.78*	2.39
12 month	28.33*	2.96

$F_{9,72}=38.7$; $p<0.0001$

* $p<0.005$ vs basal (Bonferroni)

Table 5. Mean change in reduction (%) of central macular thickness from baseline for Central Retinal Vein Occlusion

Time	Mean	s.d.
1 week	-52.9*	13.7
1 month	-34.3*	17.4
2 month	-36.1*	12.3
3 month	-35.0*	11.5
3 month+1wk	-60.4*	9.8
6 month	-23.8*	11.0
6 month+1wk	-60.5*	12.4
9 month	-35.5*	15.4
9 month+1 wk	-61.1*	11.7
12 month	-56.1*	6.5

Table 6. Mean change in ETDRS letter score from baseline for Branch Retinal Vein Occlusion

Time	Mean	s.d.
basal	39.0	14.9
1 week	58.5*	10.9
1 month	47.6	7.1
2 month	47	6.8
3 month	41.7	14.9
3 month+1wk	52.6	5.7
6 month	43.9	11.1
6 month+1wk	66.9*	7.6
9 month	50.9	12.8
9 month+1 wk	64.1*	11.4
12 month	64.2*	11.9

$F_{9,63}=8.04$; $p<0.001$

* $p<0.005$ vs basal (Bonferroni)

Table 7. Mean change in reading time from baseline for Branch Retinal Vein Occlusion

Time	Mean	s.d.
basal	7.7	3.1
1 week	5.6	1.7
1 month	6.7	3.0
2 month	6.9	2.5
3 month	8.7	6.7
3 month+1wk	3.7*	0.6
6 month	7.3	3.4
6 month+1wk	3.4*	0.5
9 month	5.9	2.1
9 month+1 wk	3.7*	0.9
12 month	4.0*	0.8

$F_{9,63}=6.25; p<0.001$

* $p<0.005$ vs basal (Bonferroni)

Table 8. Mean change in number of letter on contrast sensitivity from baseline for Branch Retinal Vein Occlusion

Time	Mean	s.d.
basal	18.62	9.39
1 week	26.75	5.55
1 month	29.50	2.73
2 month	23.9	3.90
3 month	21.25	2.31
3 month+1wk	26.88	1.73
6 month	23.25	4.23
6 month+1wk	26.50	5.35
9 month	28.13	4.32
9 month+1 wk	30.88*	1.36
12 month	27.88	2.03

$F_{9,63}=6.86$; $p<0.001$

* $p<0.005$ vs basal (Bonferroni)

Table 9. Mean change in reduction (%) of central macular thickness from baseline for Branch Retinal Vein Occlusion

Time	Mean	s.d.
1 week	-42.5	20.3
1 month	-36.2*	17.6
2 month	-31.7*	14.2
3 month	-18.1	18.1
3 month+1wk	-50.7*	11.1
6 month	-29.4*	13.3
6 month+1wk	-54.1*	11.4
9 month	-35.4*	18.2
9 month+1 wk	-62.7*	9.4
12 month	-48.5*	15..8

T. coli 10⁴ to 10⁵

T. coli 10⁴ to 10⁵ (Baseline)

T. coli 10² to 10³

T. coli 10² to 10³ (Baseline)

Figure 1 (n=100)

Frequency: total driving

Figure 2 (n=100)

Frequency: total driving

Height (m) (m)

Logarithmic multi-height values

Height (m) (m)

Logarithmic multi-height values

Figure 10 (a) with 100000

Note: 100000 transfer volume

Figure 10 (b) with 100000

Note: 100000 transfer volume