Branch Retinal Vein Occlusion: Updated Therapy by Lucentis

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ABSTRACT
Branch retinal vein occlusion (BRVO) is a common retinal vascular disorder with the potential for significant vision-related morbidity. The disease entity has long been known, but until recently, there has been no effective treatment besides grid laser photocoagulation, which reduces edema very slowly and provides benefit in some, but not all patients. Various new therapeutic approaches have been developed in the past few years, recently by Vascular Endothelial Growth Factor (VEGF) inhibitors. The objective of this review is to evaluate the commonly advocated treatment by Lucentis as a VEGF inhibitor in the light of our current scientific knowledge of BRVO.

Keywords: branch retinal vein occlusion, vascular endothelial growth factor inhibitors, lucentis

INTRODUCTION
Branch retinal vein occlusion (BRVO) is the most common retinal vascular disorder after diabetic retinopathy and is a significant cause of visual handicap [1,2]. BRVO is more common than central retinal vein occlusion, with a 5-year incidence in 0.6% of the general population, compared with a 0.2% 5-year incidence of central retinal vein occlusion (CRVO) [3]. The 9-year cumulative incidence of BRVO was 2.7% for BRVO and 0.3% for CRVO in a General Japanese Population [4]. In a recent analysis of pooled data from population studies worldwide, the overall retinal vein occlusion (RVO) prevalence was 0.52% (0.44% branch retinal vein occlusion (BRVO), 0.08% central retinal vein occlusion (CRVO), translating to approximately 16 million individuals worldwide affected by RVO [5]. The first case of BRVO was reported by Leber in 1877. There are still gaps in understanding the etiology and pathogenesis of circulatory disorders of the branches of central retinal vein. Possible causes of BRVO include external vascular compression, disease of the vein wall, or intravascular thrombus formation [6]. Hypertension and atherosclerosis are known risk factors for BRVO, and both cause thickening of arteriole walls. BRVO occurs at sites where retinal arterioles cross over veins and it appears that thickening of the arteriole wall compresses the vein, causes turbulent flow, damages endothelium, and promotes thrombosis. The obstruction is located in one of the branches of the central vein, affecting only part of the posterior pole and the portion of the peripheral retina drained by occluded branch [3]. The obstruction in venous outflow after BRVO increases intraluminal venous pressure and causes transudation of plasma and blood, resulting in edema, including macular edema and hemorrhages throughout the drainage area of a branch retinal vein. Severe edema appears to increase interstitial pressure and compromise arterial perfusion resulting in variable amounts of capillary occlusion and cotton wool patches. It is likely that differences in the amount of pre-existent arterial insufficiency from atherosclerosis determines differences in the amount of capillary nonperfusion. Extensive nonperfusion is associated with a poor prognosis. In some patients, ischemia increases over time and they are viewed as undergoing a transition from nonischemic to ischemic. Severe retinal ischemia can be complicated by retinal neovascularization, neovascular glaucoma, and a very poor visual outcome.

Previously, the only treatment for this retinal vascular disease was grid laser photocoagulation, which reduces edema very slowly and provides benefit in some, but not all patients. Lately, however, treatment paradigms have been changing. Branch retinal vein occlusion leads to retinal ischaemia, which then induces upregulation of various inflammatory factors, including vascular endothelial growth factor (VEGF), which is also known to play a role in macular edema (ME) secondary to retinal vein occlusion [7]. Observations by Noma et al.[8,9] suggest that in patients with BRVO, vascular occlusion induces the
expression of vascular endothelial growth factor (VEGF) and Interleukin-6 (IL-6), resulting in blood-retinal barrier breakdown and increased vascular permeability. Thus, VEGF and IL-6 may contribute to the development and progression of vasogenic (ME) in BRVO.

Branch retinal vein occlusion is associated with increased levels of vascular endothelial growth factor (VEGF), and therapy by anti-angiogenics or vascular endothelial growth factor inhibitors (anti-VEGF) was proposed to be a promising strategy for branch retinal vein occlusion. Consequently, several anti-angiogenics have been developed for the treatment of vasocclusive disease of retinal vein. Intraocular injections of a VEGF-binding protein reduce vascular leakage, resulting in improvement in macular edema, accelerate resorption of retinal hemorrhages, and prevent worsening of capillary nonperfusion [10,11].

The objective of this review is to evaluate the commonly advocated treatment by Lucentis as a VEGF inhibitor in the light of our current scientific knowledge of BRVO.

**LUCENTIS**

In June 2006, Lucentis (ranibizumab, Roche/Genentech) has first received FDA approval for the treatment of macular edema due to BRVO.

Ranibizumab is a humanized, affinity-matured VEGF antibody fragment that binds to and neutralizes all isoforms of VEGF.

One phase III multicenter, prospective clinical trial assessing the safety, tolerability and efficacy of intravitreal ranibizumab injections in the treatment of macular edema secondary to BRVO was finished. It was called BRAVO (study of the efficacy and safety of ranibizumab injection compared with sham in patients with macular edema due to BRVO) [12].

In the BRAVO study, 397 patients with macular edema following branch retinal vein occlusion (BRVO) were randomized to receive monthly intraocular injections of 0.3 mg (n = 134) or 0.5 mg (n = 131) of ranibizumab or sham injections (n = 132). Patients were eligible if they had foveal-involved macular edema from a BRVO occurring within 12 months of study entry, best corrected visual acuity (BCVA) of 20/40 to 20/400, and center subfield thickness (CST) ≥ 250 μm (Stratus OCT3). Patients were excluded if they had a brisk afferent pupil defect, had scatter laser photocoagulation within 3 months, an intraocular injection of steroid or a VEGF antagonist within 3 months, or had an improvement of ≥10 ETDRS letters in BCVA between screening and baseline. Baseline characteristics were well balanced among the three groups; mean BCVA was 20/80, the mean time from diagnosis of BRVO was 3.5 months, and the mean center point thickness (CPT) was 520 μm. Starting at month 3, patients were eligible for grid laser treatment if hemorrhages had cleared sufficiently to allow safe application of laser and the following criteria were met: Snellen equivalent BCVA ≤ 20/40 or mean CST ≥ 250 μm, and compared with the visit 3 months before the current visit, the patient had a gain of <5 letters in BCVA or a decrease of <50 μm in mean CST. If rescue laser was not given at month 3, the same criteria were applied at month 4, and if rescue laser was not given at month 4, the criteria were applied at month 5.

At month 6, the primary endpoint, mean change from baseline BCVA letter score was 16.6 and 18.3 in the 0.3 mg and 0.5 mg ranibizumab groups and 7.3 in the sham group (P < 0.0001). The percentage of patients who gained ≥ 15 letters in BCVA was 55.2% (0.3 mg) and 61.1% (0.5 mg) in the ranibizumab groups and 28.8% in the sham group (P < 0.0001). The percentage of patients with a Snellen equivalent BCVA of 20/40 or better was 67.9% (0.3 mg) and 64.9% (0.5 mg) compared with 41.7% in the sham group (P < 0.0001). The percentage of patients with a Snellen equivalent BCVA of 20/200 or worse was 15% (0.3 mg) and 0.8% (0.5 mg) compared with 9.1% in the sham group (P < 0.01). Based upon the 25-item National Eye Institute Visual Function Questionnaire NEI VFQ-25 survey, patients who received ranibizumab felt they had greater improvement (improvement from baseline in NEI VFQ score: 9.3, 0.3 mg; 10.4, 0.5 mg: 5.4, sham). There was greater reduction of macular edema in the ranibizumab groups because CPT was reduced by 337.3 μm (0.3 mg) and 345.2 μm (0.5 mg) compared to 157.7 μm in the sham group. The percentage of patients with CPT ≤ 250 μm at month 6 was 91% (0.3 mg), 84.7% (0.5 mg), and 45.5% (sham, P < 0.0001). More patients in the sham group (54.5%) received rescue grid laser therapy than in the 0.3 mg (18.7%) or 0.5 mg (19.8%) ranibizumab groups. There were no safety signals identified in this trial.

After the primary endpoint in the BRAVO trial, patients were evaluated every month and if study eye Snellen equivalent BCVA was ≤20/40 or mean CST was ≥250 μm, they received an injection of ranibizumab; patients in the ranibizumab groups received their assigned dose and patients in the sham group received 0.5 mg. In patients with BRVO, the mean number of ranibizumab injections during the observation period was 2.9, 2.8, and 3.8 in the 0.3 mg, 0.5 mg, and sham/0.5 mg groups; and the percentage of patients that did not receive any injections during the observation period was 17.2, 20.0, and 6.5, respectively [13]. At month 12 in the ranibizumab groups, the improvement from baseline in
ETDRS letter score was 16.4 (0.3 mg) and 18.3 (0.5 mg), very similar to the month 6 results, indicating that vision is well maintained when injections are given only if there is recurrent or residual macular edema. Patients in the sham group showed substantial improvement during the observation period when they were able to receive ranibizumab; improvement from baseline in letter score was 7.3 at month 6 and 12.1 at month 12. The percentage of patients who had an improvement from baseline BCVA letter score ≥ 15 at month 12 was 55.2% (0.3 mg) and 61.1% (0.5 mg) in the ranibizumab groups, almost identical to the month 6 results. In the sham group, 43.9% of patients improved from baseline ≥ 15 in letter score at month 12 compared to 28.8% at month 6. At month 12, 67.9% (0.3 mg) and 64.4% (0.5 mg) of patients in the ranibizumab groups had a Snellen equivalent BCVA of 20/40 compared to 56.8% in the sham/0.5 mg group. Thus, in BRAVO study, patients in the sham groups showed a substantial improvement in vision during the second 6 months when they were able to receive ranibizumab as needed, but their vision at month 12 was not as good as that in patients in the ranibizumab groups [14]. This raises a question as to whether delay in treatment carries a visual penalty.

The results from open-label extension trial of the 12-month Ranibizumab assessing long-term safety and efficacy in BRAVO trial [15] evidenced that in patients who completed month 12, the mean number of injections (excluding month 12 injection) in the sham/0.5-,-0.3/0.5-,- and 0.5-mg groups was 2.0, 2.4, and 2.1 (branch RVO). The incidence of study eye ocular serious adverse events and systemic adverse events potentially related to systemic vascular endothelial growth factor inhibition across treatment arms was 2% to 9% and 1% to 6%, respectively. The mean change from baseline BCVA letter score at month 12 in branch RVO patients was 0.9 (sham/0.5 mg), -2.3 (0.3/0.5 mg), and -0.7 (0.5 mg), respectively. The authors concluded that no new safety events were identified with long-term use of ranibizumab; rates of systemic adverse events potentially related to treatment were consistent with prior ranibizumab trials. Results suggest that during the second year of ranibizumab treatment vision in branch RVO patients remained stable, follow-up and injections should be individualized. In addition, the subanalyses in BRAVO study [12,16] generally confirmed that patients with BRVO who were younger or who had worse vision and greater retinal thickness at baseline fared better. Patients with BRVO fared better if time from diagnosis to treatment was less than 3 months.

In general, then, in BRVO, patients who needed fewer therapies, such as laser or other previous treatments, probably had milder RVO requiring less treatment. Patients who were younger did better than those who were older [17].

Clinical evaluation of ranibizumab (Lucentis, Novartis) based on two double-blind randomised trials comparing ranibizumab (0.3 mg or 0.5 mg) versus placebo in a total of 795 patients revealed that the incidence of heart failure and transient ischaemic attacks was higher during the second year of ranibizumab therapy than during the first year of treatment [18]. Patients should be informed of the potential adverse effects and uncertainties and be reminded that this condition improves spontaneously in about 50% of cases [18], or almost in one quarter of affected eyes at 3 years [19], further controlled and prospective studies are necessary to compare treatment by Lucentis to the natural course with a longer follow-up [19].

There is some evidence that intravitreal anti-VEGF injections may result in systemic absorption, with the potential for injury in organs that are reliant on VEGF, such as the kidney. Pellé et al. [20] reported the first case of a patient who developed an acute decrease in kidney function, nonimmune microangiopathic haemolytic anaemia with schistocytes, and thrombocytopenia after 4 intravitreal injections of ranibizumab. Light microscopy of a kidney biopsy specimen showed segmental duplications of glomerular basement membranes with endothelial swelling and several recanalized arteriolar thrombi. Because of the increasing use of intravitreal anti-VEGF agents, ophthalmologists and nephrologists should be aware of the associated risk of kidney disease. Early detection is crucial so that intravitreal injections can be stopped before severe kidney disease occurs. In Sorensen and Sheibani [21] opinion perhaps baseline and renal function during treatment (serum creatinine and urinary protein levels, blood pressure) should be carefully monitored to ensure that the improved visual acuity is not at the expense of renal function.

Anti-VEGF therapy may therefore have adverse effects on ocular blood flow. Von Hanno et al. [22] presented two cases of retinal artery occlusion after intravitreal injection of bevacizumab (Avastin) and ranibizumab (Lucentis) respectively and concluded that the therapeutic principle may be associated with an increased risk of retinal arterial occlusions.

The worldwide use of intravitreal application of anti-vascular growth factor and the realisation that regular applications over long periods of time are necessary to maintain vision in these eyes, has revealed the problem of tolerance/tachyphylaxis [23]. In 2008, a paper suggested for the first time possible tachyphylaxis/tolerance with chronic ranibizumab [24]. Binder S. [23] recommended different options to prevent tachyphylaxis/tolerance: (1) to increase the dosage or shorten treatment intervals if tolerance has developed; (2) to pause treatment if tachyphylaxis has occurred; (3) to combine drugs with different
modes of action; or (4) to switch to a similar drug with different properties (bevacizumab and ranibizumab differ in molecular size, affinity and absorption).

An important disadvantage of anti-VEGF drugs is the need for frequent reinjections and even more frequent control visits. Further advances are needed in order to improve quality of life and reduce the burden to healthcare systems[25].

The associated increase in clinical workload has been substantial and there is concern that the introduction of anti-VEGF treatments for BRVO could further exacerbate pressure on clinic capacity in the hospital eye service [26].

In conclusion, the available randomized clinical trials evidence suggests that repeated treatment of non-ischaemic macular edema secondary to BRVO with the anti-VEGF agent ranibizumab may improve clinical and visual outcomes at six and 12 months. However, the frequency of re-treatment has not yet been determined and the impact of prior or combined treatment with laser photocoagulation on the primary outcome is unclear. Results from ongoing studies should assess not only treatment efficacy but also, the number of injections needed for maintenance and long-term safety and the effect of any prior treatment [27].

CONCLUSION

The development of therapy with anti-angiogenics or vascular endothelial growth factor inhibitors (anti-VEGF) has marked the beginning of a new era in eye diseases treatment. As elevated intraocular levels of VEGF have been demonstrated in patients with retinal vein occlusions there is a strong basis for the hypothesis that anti-VEGF agents may be beneficial in the treatment of vascular leakage and macular edema in BRVO.

In spite of the fact that pharmacotherapy by Lucentis in branch retinal vein occlusion is a clear breakthrough with exciting potential there are still many unclear points, such as: the correct time to start injections and the specific moment to finish them, the number of injections, the long-term efficacy and safety, ocular and systemic side effects.

Individualized treatment allows the identification of patients who are most likely to benefit from the treatment. Tailoring treatment to the individual patient in this way should increase the chance of treatment success, while sparing patients from unnecessary drug exposure and risk of adverse events. Furthermore, avoiding unnecessary treatment also has the potential to improve the cost-effectiveness of treatment.

REFERENCES


**HOW TO CITE THIS ARTICLE**