Intravitreal Ranibizumab (Lucentis®) for the Treatment of Macular Edema of Central and Branch Retinal Vein Occlusion

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ABSTRACT

Purpose: To evaluate the safety and efficacy of intravitreal ranibizumab (Lucentis®) in the treatment of Macular Edema associated with central and branch retinal vein occlusion.

Methods: Retrospective study of 24 eyes, 12 with CRVO and 12 with BRVO, treated with intravitreal ranibizumab as a monotherapy. Inclusion criteria included decreased VA, loss of the foveal depression, central foveal thickness (CFT) >300 μm and, for BRVO without previous laser photocoagulation, extensive macular hemorrhages. The evaluation of best corrected visual acuity (BCVA) (ETDRS chart) and macular edema (ME) (OCT) was performed each 4 to 6 weeks.

Results: After a mean follow-up of 296 days (range 80-556) and a mean number of 6,2 injections, BRVO eyes showed a mean global improvement of 16,42 letters in BCVA (p= 0,0024) and a mean CFT reduction of 48,5%, from 605,9μm (σ =266,3) to 312,3μm (σ =98), (p= 0,0076). CRVO eyes improved 10,75 letters in BCVA (p= 0,0077), after a mean follow-up of 435 days (range 76-920). A mean number of 8,8 injections, enabled, as well, a mean CFT reduction of 55,5%, from 700,8μm (σ =177,8) to 312μm (σ =162,9), (p= 0,0004). One eye from the CRVO group developed iris neovascularization despite ranibizumab injections.

Conclusions: Intravitreal ranibizumab injections have shown short-term promising results in BRVO and CRVO with a 2 lines BCVA improvement and a decrease in CFT. Randomized studies are necessary to validate these apparently good results.

INTRODUCTION

Retinal vein occlusion (RVO) is the second most common common vascular disorder of the retina and can lead to severe visual loss. The complications of BRVO are similar to those for CRVO but more limited in scope, because only part of the retina is drained by the involved branch vein. Since the area of ischemic retina tends to be much less than that in patients with CRVO, iris neovascularization and neovascular glaucoma are rare, but retinal NV adjacent to the ischemic retina can occur. The most common cause of reduced vision in both cases is macular edema, but nonperfusion of perifoveal capillaries can also be another contributing factor.

The Central Retinal Vein Occlusion Study was a large multicenter trial that investigated the effect of grid laser photocoagulation in patients with macular edema due to CRVO, and found no difference in the final VA in treated patients (VA=20/200) versus in untreated patients (VA=20/160). On the other hand, laser photocoagulation, as demonstrated by the Branch Vein Occlusion Study, represents the gold standard for the treatment of macular edema and ocular neovascularization following BRVO.
Thus, in both CRVO and BRVO, retinal ischemia occurs and serves as an exacerbating factor. The ischemic retina releases vascular endothelial growth factor (VEGF) which underlies neovascular complications, but also causes excessive vascular permeability. Hence, the release of VEGF is likely to contribute to macular edema.

The limited functional outcomes achievable by means of laser treatment have prompted researchers to try alternative options, with varying results. Vascular endothelial growth factor inhibitors have recently been employed to neutralize the effects of VEGF. VEGF is a key mediator of intraocular NV and ME. It is triggered by retinal hypoxia, and aqueous levels of VEGF are correlated with the degree of retinal ischemia and the severity of ME in BRVO. Recently, the Food and Drug Administration (FDA) approved in the USA the use of Ranibizumab injection (Lucentis®) for the treatment of Macular Edema following retinal vein occlusion, based on the outcome of the BRAVO and CRUISE studies.

Our purpose with this study was to evaluate the safety and efficacy of intravitreal ranibizumab (Lucentis®), as monotherapy, in the treatment of Macular Edema associated with CRVO and BRVO.

METHODS

We performed a retrospective, non randomized, interventional case series of twenty-four eyes with ME secondary to retinal vein occlusion, 12 with central retinal vein occlusion [Figure 1, 2] and 12 with branch retinal vein occlusion [Figure 3, 4].

![Fig. 1 and 2 | CRVO.](image)

![Fig. 3 and 4 | BRVO.](image)
Twelve patients were male and twelve were female. In CRVO group, 91.7% of the patients (N=11) were male, whereas in BRVO group 91.7% (N=11) were female. Main inclusion criteria were best corrected visual acuity (BCVA) under 20/32 (Early Treatment Diabetic Retinopathy Study chart - ETDRS); loss of the foveal depression; ME involving the centre of the fovea with a minimum central foveal thickness (CFT) at baseline of >300 mm and for BRVO patients, the presence of extensive macular hemorrhages.

All patients were naïve to treatment of ME. Patients were excluded if previous vitreoretinal surgery, intravitreal injections or laser treatment had been performed. Patients with neovascularization at baseline were not included.

Intravitreal injections of ranibizumab (0.5 mg) were performed under sterile conditions. Loading dose was not assessed. Written informed consent was obtained.

Follow-up examinations were carried out every 4 to 6 weeks and included ophthalmologic examination, BCVA testing (ETDRS chart) and optical coherence tomography (OCT). Criteria for reinjection were loss of the foveal depression and CFT >300 mm. Main outcome measures were VA and CFT. We considered VA improvement as a gain of ≥ 1 letter, worsening as a loss of ≥ 1 letter and unchanged if VA was equal both at baseline and at the end of follow-up.

Follow-up and baseline data were compared using the paired t-test. The level of statistical significance was set at p<0.05.

RESULTS

Intravitreal injections of ranibizumab were tolerated well with no inflammation or other problems. None of the patients showed elevation of blood pressure, thromboembolic events, or any other systemic problems.

For CRVO group, the mean age was 60.3 years (range 36-80) and the mean follow-up was 435 days (range 76-920). The mean time elapsed between de diagnosis and the first injection was 38 days (range 11–71), and between injections 68 days (range46.5–105). These patients received an average of 8.8± 3.3 injections (range 1-11) and a total of 57 injections were performed.

For BRVO group, the mean age was 69.3 years (range 60-78) and the mean follow-up was 296 days (range 80-556). The mean time elapsed between de diagnosis and the first injection was 40 days (range 9–81), and between injections 72 days (range 47–88.3). These patients received an average of 6.2 ± 1.6 injections (range 1-6) and a total of 40 injections were performed.

Ranibizumab treatment resulted in significant reduction of ME and improvement of VA in CRVO and BRVO at last visit.

Effect of ranibizumab on visual acuity

In a general way, the treatment with ranibizumab resulted in a BCVA improvement in 66.6% and 83.4% of the eyes, in CRVO and BRVO group, respectively. 16.7% of CRVO patients unchanged BCVA and 16.7% worsened BCVA. For BRVO patients, 8.3% unchanged and 8.3% worsened BCVA [Graphic 1, 2].

Graph. 1 | Global effect of ranibizumab on BCVA (CRVO).

Graph. 2 | Global effect of ranibizumab on BCVA (BRVO).
Mean BCVA at baseline was 36.5 letters (range 5-75) in patients with CRVO and 35.9 (5-60) in patients with BRVO. Mean BCVA at the end of the follow-up was 47.25 letters (range 5-85) for CRVO group and 52.33 letters (range 25-77) for BRVO, so with a BCVA improvement of 10.75 letters (range -10 to +30) to CRVO (p= 0.0077) and 16.42 letters (range -10 to +39) to BRVO group (p= 0.0024) [Graphics 3]. There was a mean change in BCVA $\geq 10$ ETDRS letters among 6 CRVO patients (50%) and $\geq 15$ letters in 8 BRVO patients (66.7%).

Graph. 3 | BCVA changes in CRVO and BRVO: from baseline to the end of the follow-up.

If we analyze the individual variation of VA during the follow-up (which was different between patients), and creating a trend line, it’s evident that for CRVO group there is a slow VA improvement over the time [Graphic 4], while for BRVO group there is a more marked slope of the trend line, so reflecting a faster improvement of VA for these patients [Graphic 5].

Graph. 4 | Individual variation of BCVA in CRVO group.

**Effect of ranibizumab on central foveal thickening**

Although the response varied somewhat among patients in each group, most showed substantial reduction in central retinal thickness over time, with a general improvement on CFT of 91.7%, in both CRVO and BRVO groups [Graphics 6, 7].

In CRVO group, the mean CFT decreased from 700.8±177.8 μm (range 377-978 μm) at baseline to 312±162.9 μm (range 155-747 μm) (p= 0.0004), thus eliminating 55.5% of the edema. In BRVO group, the mean CFT at baseline of 605.9±266.3 μm (range 348-1137 μm) improved to 312.3±98 μm (range 190-536 μm) (p= 0.0076), thus eliminating 48.5% of the edema [Graphic 8; Figures 5, 6].
Showing the CFT changes over the time it’s possible to say that the results are similar to those obtained for VA, with a slower improvement registered for CRVO comparatively to BRVO group [Graphics 9, 10]. In a general way, all the patients in both groups, tended to show rapid response after the first injection of ranibizumab, with further improvement after subsequent injections. The response seemed to be more sustained for BRVO patients, once that 4 patients from CRVO group showed a worsening of the thickening following the improvements [Graphics 9].

Graph. 7 | Global effect of ranibizumab on CFT (BRVO).

Graph. 8 | Global effect of ranibizumab on CFT (BRVO).

Graph. 9 | Individual variation of CFT in CRVO group.

Fig. 5 | OCT evolution among the follow-up period, in one patient with CRVO.

Fig. 6 | OCT evolution among the follow-up period, in one patient with BRVO.
On the final OCT we realized that 33.3% of the CRVO and 25% of the BRVO patients still presented macular edema [Graphic 11].

During the follow-up period, one of the twelve eyes with CRVO (8.3%) developed iris neovascularization despite the administration of two ranibizumab injections. From this patient we don’t have further information once that he decided to be treated in another center (1 drop out).

**DISCUSSION**

Although this is an uncontrolled trial involving a relatively small number of patients, the results were very consistent among patients and suggest that intraocular injections of ranibizumab as monotherapy have a substantial effect on visual acuity an on macular edema in retina vein occlusions.

**CRVO**

The Central Retinal Vein Occlusion Study was a large multicenter trial that investigated the effect of grid laser photocoagulation in patients with macular edema due to CRVO [14]. Although 69% of patients in the treated group compared to 0% in the untreated group showed reduction of fluorescein leakage in the macula at the end of 1 year, there was no difference in the final VA (20/200 in treated patients versus 20/160 in untreated patients). It has been felt that a possible explanation is that chronic edema due to CRVO leads to permanent visual loss. Our data demonstrate that visual improvement is possible. In addition to grid laser therapy, several treatments have been tried in patients with macular edema due to CRVO including the use of anticoagulants, fibrinolytics, steroids, acetozolamide, iso-volemic hemodilution, surgically induced retinochoroidal anastamoses or laser-induced retinochoroidal anastamoses, and radial optic neurotomy. A recent meta-analysis of all published randomized clinical trials concluded that there is no convincing evidence that any of these treatments provide benefit15.

The natural history of CRVO is well known and it was examined as part of the collaborative Central Retinal Vein Occlusion Study: rarity of spontaneous improvements in patients with macular edema due to CRVO. Even if our series did not have a control group, the functional outcomes of our patients seemed to be better than those previously reported with alternative therapeutic approaches, although eligibility criteria differed among studies.

**BRVO**

In contrast, the gold standard for the treatment of the 2 main complications related to BRVO (NV and ME) is laser photocoagulation, as stated by the Branch Vein Occlusion Study. Grid laser therapy provides modest benefit in patients with macular edema due to BRVO16; after 3 years, patients treated with grid laser photocoagulation improved by 1.33 lines from baseline compared to an improvement of 0.23 lines in the control group. Unfortunately, the Branch Vein Occlusion Study only took into consideration a fraction of BRVO cases. Indeed, inclusion criteria of the investigation allowed the enrolment only when visual acuity was under 20/40; there was no evidence of retinal ischemia, and no hemorrhage within the foveal region. Thus, recalling that ischemic BRVO can reach about two thirds of cases3, no indication could be obtained for the majority of cases. A study analyzed the natural history of ischemic BRVO, revealing that a spontaneous improvement in visual acuity 1 line can be recorded in 91% of cases17. Moreover, even though conventional grid laser treatment is effective in
reducing ME and improving visual acuity, the results achieved are modest: a 2-line VA gain was obtained only in 65% of cases; the mean VA gain was 1.3 lines; conventional grid laser treatment may be associated with the occurrence of complications including enlargement of the laser scar, choroidal NV, subretinal fibrosis, and deterioration in visual field sensitivity.

The results of our study are very encouraging because of the magnitude and consistency of response among patients with BRVO; however, they are not definitive because of the relatively small number of patients studied, the lack of a control group, and the short follow-up.

VEGF plays an important role in the development of macular edema in retinal vein occlusions. Hemodynamic changes from the vascular occlusion lead to reduced retinal perfusion and ischemia causing increased production of VEGF. The increased production of VEGF is the major cause of macular edema, because blockade of the VEGF results in substantial improvement in the edema.

In our study no drug-related adverse effects such as elevation of blood pressure, thromboembolic events, or any other systemic problems were observed. This provides some preliminary data, suggesting that intraocular injections of ranibizumab are well-tolerated in patients with retinal vein occlusions just as they are in patients with neovascular age-related macular degeneration. Reinjections were performed only in the case of persistent or recurring ME. This treatment scheme allowed us to keep the total number of injections very low, thus minimizing the risk of endophthalmitis. Nevertheless, this strategy resulted in a highly significant improvement in CFT and VA.

Recently, the Food and Drug Administration (FDA) approved ranibizumab injections for the treatment of macular edema secondary to CRVO and BRVO, based on published data from CRUISE and BRAVO trials.

The CRUISE study assessed the safety and efficacy profile of Lucentis® (ranibizumab, Genentech) in a total of 392 patients with macular edema following central-RVO. In this study, 130 patients who received a 0.5-mg dose of ranibizumab in six monthly doses had a mean gain of 14.9 ETDRS letters from baseline and 132 patients in the 0.3-mg group had a mean gain of 12.7 letters from baseline. Patients in the sham arm of the study had a 0.8 letter gain at 6 months. Overall, 47.7%, 46.2% and 16.9%, respectively, gained 15 or more letters. So, significantly more people treated with monthly ranibizumab showed sustained vision improvement during the six-month study, with an effect seen as early as seven days and a benefit maintained throughout the 12 months of follow-up.

CONCLUSIONS

Intravitreal ranibizumab injections as monotherapy have shown short-term promising results in both CRVO and BRVO, with a mean BCVA improvement of 11 letters for CRVO patients and 16 letters for BRVO patients, as well as a decrease of central foveal thickness.

Further randomized studies are needed in order to clarify the proper point for onset and end of the treatment, and to standardize the intervals between injections. The complex genesis of these diseases and their variable progression makes it difficult to find a common treatment scheme. Moreover, these studies will have to show whether the positive results of the anti-VEGF therapy are only transient or may finally lead to long-lasting stabilization.

Retinal vein occlusions are a complex vascular disorder, the appropriate therapy of which is still uncertain. A clinical research based on randomized clinical trials instead of case series, will provide reliable information regarding the best therapeutic approach for every form of CRVO and BRVO in the near future.

REFERENCES


