

# Anti-VEGF in Treatment of Central Retinal Vein Occlusion

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## ABSTRACT

*Macular edema along with macular ischemia is responsible for decreased visual acuity in central retinal vein occlusion. Bevacizumab (Avastin, Genentech) blocks vascular endothelial growth factor (VEGF) induced hyperpermeability of blood vessels. In this prospective case series we investigated the efficacy of anti-VEGF treatment in reduction of central retinal thickness (CRT) and improvement in visual acuity (VA). 25 patients were followed up for 12 months and treated monthly with intravitreal bevacizumab. VA and CRT were measured at each visit. Treatment was discontinued as the peak improvement of either parameter was reached and reinstated in case of deterioration/recurrence of edema. Study endpoints included: VA using ETDRS charts, CRT and number of injections at 12 months. Mean VA from all 25 patients increased by 3.1 logMAR lines ( $p < 0.05$  compared to baseline). The improvement of VA after bevacizumab injection was in correlation with a decrease in CRT. In subgroup analyses, patients receiving bevacizumab injection within the first 3 months after CRVO showed an average VA gain of 4.2 logMAR lines. Mean of 4.5 injections was needed to control the disease during the follow-up period. Bevacizumab treatment was effective in VA and reducing CRT. It appears from subgroup analysis that initiation of treatment early in the course of disease produced better functional outcome. Several injections were needed to control the disease. Regular OCT examinations and retreatment are advised in order to maintain initially reached VA.*

**Key words:** central retinal vein occlusion, macular edema, anti-vascular endothelial growth factor therapy, bevacizumab

## Introduction

Central retinal vein occlusion (CRVO) is a retinal vascular condition that may cause significant ocular morbidity. It is the second most common retinal vascular disorder, after diabetic retinopathy, affecting men and women equally and occurring predominantly after the age of 65. The prevalence of CRVO is estimated to be 0.1 to 0.4% in general population<sup>1,2</sup>, but both incidence and prevalence increases with age. CRVO is usually unilateral disease, but up to 7% of patients may develop any form of retinal vascular occlusion in the fellow eye within 5 years from the onset of occlusion in the first eye<sup>3–5</sup>. CRVO has been associated with various systemic and ocular pathologic conditions including: hypertension, diabetes mellitus, cardiovascular disorders, bleeding and clotting disorders, vasculitis, autoimmune disorders, use of oral contraceptives, closed-head trauma, alcohol consumption, primary open-angle or angle-closure glaucoma. CRVO

can be divided into 2 clinical types: ischemic and non-ischemic. A number of patients may have an intermediate form at presentation with variable clinical course. Initially, it may be difficult to classify a given patient into either category, since CRVO may change with time. Non-ischemic CRVO is the less severe form of the disease. It may present with good vision, fewer retinal hemorrhages and cotton-wool spots, no relative afferent pupillary defect, and good retinal perfusion. Nonischemic CRVO may resolve fully with good visual outcome or may progress to the ischemic type. Ischemic CRVO is the severe form of the disease. CRVO may present initially as the ischemic type, or it may progress from nonischemic. Usually, ischemic CRVO presents with severe visual loss, extensive retinal hemorrhages and cotton-wool spots, presence of relative afferent pupillary defect, poor retinal perfusion and a presence of severe electroretinographic changes. In

addition, patients may end up with neovascular glaucoma and a painful blind eye. The pathogenesis of CRVO is not clearly understood. Histopathologic studies of eyes with CRVO demonstrated a thrombus occluding the lumen of central retinal vein at the level of lamina cribrosa<sup>6</sup>. It seems that anatomic abnormalities at the level of lamina cribrosa may be responsible for development of CRVO (compression of central retinal vein due to raised intraocular pressure, atherosclerotic changes in central retinal artery, or inflammation of the central retinal artery). Also hemodynamic changes (reduced blood flow, increased blood viscosity, altered lumen wall) may produce stagnant flow and subsequent thrombus formation in the central retinal vein. Macular edema along with macular ischemia is responsible for decreased visual acuity in central retinal vein occlusion. Bevacizumab (Avastin, Genentech) blocks vascular endothelial growth factor (VEGF) induced hyperpermeability of blood vessels. In this prospective case series we investigated the efficacy of anti-VEGF treatment in reduction of central retinal thickness (CRT) and improvement in visual acuity (VA).

## Materials and methods

25 patients were followed up for 12 months and treated monthly with intravitreal bevacizumab. On each examination we performed slit lamp biomicroscopy to check any anterior segment abnormalities (iris neovascularization) and fundus examination was performed using non contact lens biomicroscopy. Visual acuity was tested (VA) using early treatment diabetic retinopathy study (ETDRS) chart and central retinal thickness (CRT) using Optopol SOCT 3D spectral domain optical coherence tomography (OCT). VA and OCT were measured at each visit. Also at initial examination we performed fluorescein angiography to each patient. Treatment was discontinued as the peak improvement of either parameter was reached and reinstated in case of deterioration/recurrence of edema. Study endpoints included: mean VA (logMAR), mean CRT and mean number of injections at 12 months. All intravitreal injections were performed under sterile conditions in the operating room. Bevacizumab was injected via the pars plana using 30 gauge needle. Then the results were compared to baseline values and statistically analyzed to see whether there is a significant change in VA and CRT when compared to baseline values.

### *Statistical analysis.*

The data was analyzed by using nonparametric student t-test to determine significance between means. The data was considered statistically significant for  $p < 0.05$ .

## Results

At 12 months follow-up visit the mean baseline VA increased by 3.1 lines from 1.03 logMar to 0.72 logMAR (12 months). At the same time mean CRT decreased from

560 microns to 259 microns. In sub-group analysis, patients receiving bevacizumab injections within the first 3 months after the onset of CRVO showed the greatest visual recovery gaining an average of 4.2 logMAR units.

Mean of 4.5 injections was needed to control the disease during the follow-up period. After 12 months of follow-up no severe ocular (endophthalmitis, retinal detachment, uveitis) or systemic adverse events were noticed. No patient developed disc, iris or retinal neovascularization.

## Discussion

Central retinal vein occlusion is the 2<sup>nd</sup> most common retinal vascular disorder affecting both men and women, causing irreversible loss of visual function. Up to now there is no clear algorithm how to manage the patients with this disease. Central retinal vein occlusion study (CVOS), which was a large, multicentric, prospective, and randomised study concluded that panretinal photocoagulation was to be performed only in case of ocular neovascularization (NVD, NVE, iris neovascularization) could be detected. The study also reported there is no benefit of grid laser photocoagulation in treatment of macular edema in eyes with VA 20/50 or worse as there was no significant difference in mean visual acuity between treated and untreated eyes. This means that laser could not improve visual acuity (resolve macular edema), but only stabilize or induce regression of neovascularization<sup>3</sup>. SCORE study compared efficacy and safety of 1-mg and 4-mg of intravitreal triamcinolone versus standard care (observation) for eyes with visual loss associated with macular edema secondary to CRVO and BRVO. Patients in the corticosteroid medication groups received an average of two injections in the first 12 months of the study. After one year, 27 % of patients in the 1 milligram group and 26 % of patients in the 4 milligram group experienced a substantial visual gain of 3 or more lines. Only 7 % of patients in the observation group experienced a similar visual gain. Therefore, patients in the corticosteroid treatment groups were five times more likely to have a substantial visual gain at one year. However, the rates of adverse events (particularly elevated intraocular pressure and cataract) were highest in the 4-mg group. Occlusion of central retinal vein causes stagnation of the blood flow and ischemic damage to the retina. Green and colleagues demonstrated inner retinal ischemic changes in 25% of eyes enucleated for CRVO. It has been postulated that ischemic damage to the retina increased production of vascular endothelial growth factor (VEGF) in the vitreous cavity, and VEGF has been implicated in the development of neovascular complications of CRVO (both anterior, posterior neovascularization and macular edema.). In a study of enucleated eyes with CRVO and neovascular glaucoma, intraretinal VEGF production from areas of ischemic retina was demonstrated<sup>7</sup>. Also, aqueous VEGF levels increase prior to the development of neovascularization of the retina (NVD, NVE, iris neovascularization) and decrease with regression of retinal

neovascularization after panretinal laser photocoagulation<sup>8</sup>. VEGF also causes capillary leakage leading to macular edema, which is the leading cause of visual cause in both ischemic and nonischemic CRVO. There are numerous case reports and small studies showing both efficacy and safety of intravitreal anti-VEGF drugs (bevacizumab and ranibizumab) in therapy of macular edema and retinal neovascularization in CRVO. BRAVO and CRUISE were the first large clinical trials confirming efficacy of anti-VEGF drugs in CRVO and branch RVO. BRAVO was a multicenter, randomized, double-masked, sham injection-controlled Phase III study of 397 patients designed to assess the safety and efficacy profile of Lucentis (ranibizumab) in treatment of macular edema secondary to branch-RVO. 55.2 % of patients who received 0.3 mg of Lucentis and 61.1 % who received 0.5 mg of Lucentis had their vision improved by 15 letters comparing to 28.8 % of patients receiving sham injections. Mean gain in BCVA was observed beginning at day seven with a 7.6 and 7.4 letter gain in the 0.3 mg and 0.5 mg study arms of Lucentis, respectively (compared with 1.9 letters in the sham injection arm).

CRUISE was a multicenter, randomized, double-masked, sham injection – controlled Phase III study designed to assess the safety and efficacy profile of Lucentis in treatment of macular edema secondary to CRVO. The study includes 392 patients and the results at six months showed 46.2 % of patients given 0.3 mg of Lucentis and 47.7 % given 0.5 mg of Lucentis improving their vision by 15 letters or more (compared to 16.9 % of patients receiving sham injections). Mean gain in BCVA was observed beginning at day seven with an 8.8 and 9.3 letter gain in the 0.3 mg and 0.5 mg study arms of Lucentis, respectively (compared with 1.1 letters in the sham injection arm). These studies showed significant improvement both in VA and resolution of macular edema after anti-VEGF therapy. In our case series we administered Ava-

stin (bevacizumab, Genentech) which has the same mechanism of action as Lucentis. VA improved by 3.1 logMAR lines and CRT decreased from 560 microns to 256 microns. Mean of 4.5 injections was needed to control the disease.

These results are consistent with the results described in other studies, showing the potential of anti-VEGF agents not only to stabilize but rather improve functional and anatomical outcome.

As the subgroup analyses showed the best gain in visual acuity was achieved in patients treated within the first 3 months after CRVO, we may recommend the therapy to be initiated as early as possible.

## Conclusion

Results from our study are compatible with those from BRAVO and CRUISE trials. We showed that bevacizumab appears to be both safe and efficient in improving VA in patients with central retinal vein occlusion. Further clinical trials with larger number of patients and longer follow-up period are needed to confirm efficacy of bevacizumab in treatment of CRVO.

Abbreviations: CRVO – central retinal vein occlusion, VEGF – vascular endothelial growth factor, CRT – central retinal thickness, VA – visual acuity, ETDRS – early treatment diabetic retinopathy study, OCT – optical coherence tomography, SOCT – spectral domain optical coherence tomography, NVD – neovascularization on disc, NVE – neovascularization elsewhere, CVOS – central retinal vein occlusion study, BRAVO – branch retinal vein occlusion study, CRUISE – efficacy and safety of ranibizumab injections in patients with macular edema secondary to central retinal vein occlusion, SCORE – standard care vs. corticosteroid for retinal vein occlusion study.

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## ANTI – VEGF TERAPIJA U LIJEČENJU OKLUZIJE CENTRALNE RETINALNE VENE

### SAŽETAK

Edem makule te ishemija makule su glavni uzročnici smanjene vidne oštrine kod okluzije centralne retinalne vene. Bevacizumab (Avastin, Genentech) blokira vaskularnim endotelnim faktorom rasta (VEGF) induciranu hiperpermeabilnost krvnih žila. U ovoj studiji istražili smo efikasnost anti – VEGF terapije u redukciji centralne retinalne debljine (CRT) i poboljšavanju vidne oštrine (VA). 25 pacijenata je praćeno 12 mjeseci i liječeno mjesečnim dozama intravitrealnog bevacizumaba. VA and CRT su mjereni prilikom svake kontrole. Liječenje je prekinuto kada je jedan od promatranih kriterija (VA i CRT) maksimalno poboljšano i ponovo nastavljena prilikom ponovne pojave edema u makuli. Promatrani ciljevi studije uključivali su: vidnu oštrinu (VA) mjerenu ETDRS tablicama, centralnu retinalnu debljinu (CRT) i broj injekcija unutar 12 mjeseci praćenja. Rezultati su pokazali da je vidna oštrina kod svih 25 pacijenata porasla za 3.1 logMAR reda ( $p < 0.05$  prema početku). Poboljšanje vidne oštrine nakon injekcije bevacizumaba bilo je u korelaciji sa smanjenjem CRT. Iz analize podataka vidjelo se da je najveće poboljšanje vidne oštrine, koje je iznosilo 4.2 logMAR reda postignuto unutar prva tri mjeseca nakon okluzije VCR. Tijekom vremena praćenja od 12 mjeseci bilo je potrebno prosječno 4.5 injekcija da bi se postigla kontrola bolesti. Injekcije bevacizumaba pokazale su se efikasne u poboljšavanju vidne oštrine i smanjenju centralne retinalne debljine. Također iz analize podataka, čini se, da raniji početak liječenja korelira s boljom krajnom vidnom oštrinom i boljim rezultatima liječenja.