Bevacizumab (Avastin) Therapy for Macular Oedema in Central Retinal Vein Occlusion – Long Term Results

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Abstract

**Background:** There is no proven treatment for vision loss in central retinal vein occlusion (CRVO). Bevacizumab has been reported in small series with limited followup to have a positive effect in reducing macular edema (CME) and improving vision in central retinal vein occlusion. We report long term results of Bevacizumab in central retinal vein occlusion.

**Methods:** Prospective interventional case series included 15 patients, serially evaluated with ETDRS BCVA, OCT, FFA and Tonometry. Results were statistically analysed.

**Results:** Mean followup was 12 +/-3.6 months (range 6 -18 months). Mean number of injections 2.2 (range 1- 4) per patient. Statistically significant reduction of macular thickness (P<0.001) was seen at 6 weeks (mean 346μ), 3months (353μ), 6months (348μ) and final followup (342μ). Significant BCVA improvement seen at 6 weeks (Mean -.27 logmar), 3 months (.3 logmar), 6 months (.15 logmar) and final followup (.21 logmar) (P=0.009). 73.3 % patients had > 2 lines of BCVA improvement at last followup.

**Conclusion:** Intravitreal Bevacizumab is an effective treatment option for CME in CRVO patients. Re-injections at appropriate timing based on the OCT findings are important for better visual outcome.

Introduction

Although central retinal vein occlusion (CRVO) is one of the most frequent retinal vascular disorders in clinical practice, its pathogenesis is still not fully understood. Green et al. ¹ found venous thrombi in nearly all rubeotic eyes after CRVO, but it remains unclear whether venous thrombus formation represents the beginning or rather the endpoint of the pathogenetic cascade.

The development of macular edema is one of the most common findings and the main reason for decreased visual acuity (VA) in early CRVO. An impaired microcirculation and reduced blood flow lead to a dysfunction of the endothelial blood-retinal barrier with increased permeability and plasma exudation into the central retina. A causative therapy to normalize the retinal perfusion is desirable, but only hemodilution therapy has shown limited benefit in randomized studies ²,³,⁴.

It seems reasonable to reduce the macular edema as soon as possible as irreversible damage of the photoreceptors occurs as early as 3 months after the development of macular edema ⁵,⁶. GRID laser photocoagulation is an evidence-based therapeutic option to reduce the macular edema in patients with branch retinal vein occlusion (BRVO), but not in central...
retinal vein occlusion (CRVO) \(^7,8\). Another option is the injection of triamcinolone (IVTA) into the vitreous cavity, which seems to be effective in early RVO. However, recent results suggest that this effectiveness is not maintained beyond 1 year despite repeated injections. The main drawback of IVTA use is the high rate of possible side effects such as glaucoma, cataract formation or endophthalmitis \(^9,10,11,12\). As in CRVO patients the macular edema is thought to be at least partly triggered by hypoxia-induced expression of vascular endothelial growth factor (VEGF) \(^13\), intravitreally administered anti-VEGF antibodies have recently been introduced into the treatment regime for RVO patients \(^14\).

Bevacizumab (Avastin, Genentech) was, along with pegaptanib, among the first anti-VEGF substances used to treat macular edema in patients with CRVO \(^15,16,17\). Initial reports on intravitreal injections of bevacizumab showed a significant reduction of central retinal thickness and improved VA \(^14,18\). To date, only retrospective studies and short term reports have been published on bevacizumab treatment of CRVO \(^14,18\). In this study we evaluate the safety, visual acuity changes and morphologic response to bevacizumab treatment in a prospective case series of CRVO patients.

### Patients and Methods

Fifteen consecutive CRVO patients with central macular oedema (CME) were included in this study.

#### Inclusion criteria

1. Funduscopically and angiographically diagnosed CRVO duration of more than 4 weeks with CME of more than 250 \(\mu\)m (measured by OCT 3, macular thickness program).
2. Best corrected VA by ETDRS equal to or worse than 0.3 Logmar (Snellen = 6/12)
3. Age older than 18 years
4. Patient able to give informed consent

#### Exclusion criteria

1. Patients with retinal, angle or disc neovascularization needing photocoagulation at first presentation
2. Other eye diseases that reduced VA
3. Not able to give informed consent
4. History of allergic reaction to bevacizumab
5. Pregnancy
6. History of Stroke/IHD/ uncontrolled HT

### Study endpoints

The primary outcome was the improvement in visual acuity (VA). Baseline visual acuity was measured using ETDRS charts a few hours prior to injection as well as on each follow-up visit (1 week and then 6 weekly after injection). For ease of comparison and purpose of statistical analysis, VA was converted to logMAR as well as Snellen equivalents.

Secondary study outcomes were:

1. Central retinal thickness measured by optical coherence tomography (OCT 3; macular thickness program)
2. Complication rate (i.e., endophthalmitis, inflammation, increased intraocular pressure, retinal tears, retinal detachment and thromboembolic events)
3. To determine the best time point for re-injection depending on the course of VA development as well as central retinal thickness.

### Patient examinations

The following data were registered: duration of CRVO before injection, ophthalmologic and medical history, patient age and sex, best corrected visual acuity (ETDRS charts) and full ocular examination including OCT and Applanation tonometry. We also documented retinal changes by color fundus photographs and fluorescein angiography (Topcon Imagenet, Japan) preoperatively and between 6 and 12 weekly after injection.

All other parameters were evaluated on the day of injection (baseline) as well as at 2 weeks and 6 weekly after injection. On each follow-up visit, possible side effects of the injection were ruled out.

### Methods

All patients underwent intravitreal injection of 1.25 mg bevacizumab (Avastin) in 0.05 ml total volume over
the inferior pars plana area, under strict aseptic precautions. After 6 weeks of follow-up time, re-injection of 1.25 mg bevacizumab was considered depending on the individual treatment response and OCT findings.

**Study design**

Our study design is that of a nonrandomized interventional case series. All patients gave their informed consent with specific emphasis on the off-label character and possible systemic side effects as well as unknown long-term ocular complications of bevacizumab.

**Statistics**

Wilcoxon Signed Ranks test was used to calculate the statistical significant difference between the paired groups. Mann Whitney-U Test was used to calculate the statistical significant difference between the two independent groups. Friedman Multiple comparison test was used to calculate the overall significance. The level of significance was 0.05 (2-sided) in all statistical testing. All these Statistical Analysis was performed using the statistical software Stata 8.1 (College Station, TX, USA).

**Results**

Table 1 displays the demographic data for all patients enrolled in this study.

<table>
<thead>
<tr>
<th>Table 1 Demographic data</th>
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<tbody>
<tr>
<td>No: of patients</td>
</tr>
<tr>
<td>Mean Age</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Duration of CRVO</td>
</tr>
<tr>
<td>Type of CRVO</td>
</tr>
</tbody>
</table>

The mean follow up was 12.2 ± 3.6 months (range - 6months to 18 months). All patients except one had completed atleast 3 months since the last injection. The mean number of injections per patient was 2.2 ± 0.884 (range – 1 to 4 injections per patient).

**Visual acuity changes**

The mean best corrected visual acuity at base line was 0.9 ± 0.31 Logmar units. Statistically significant BCVA improvement (P = 0.009) was seen at 6 weeks 0.63 ± 0.34 (Mean improvement 0.27 logmar), at 3 months 0.60 ± 0.32 (mean improvement 0.31 logmar), at 6 months 0.74 ± 0.43 (mean improvement 0.15 logmar) and final followup 0.68 ± 0.54 (mean improvement 0.21 logmar).

Overall there was a statistically significant improvement in BCVA over time (P - 0.009) -FRIEDMAN test.

73.3 % patients had 2 or more lines of visual acuity improvement and 60 % patients had 3 or more lines of improvement. Table 2 shows the visual acuity change distribution among the study patients at the final follow up.

<table>
<thead>
<tr>
<th>Table 2: Final BCVA (in logmar)</th>
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<tbody>
<tr>
<td>Frequency</td>
</tr>
<tr>
<td>&gt;2 lines improvement</td>
</tr>
<tr>
<td>&lt;=2 lines improvement</td>
</tr>
<tr>
<td>Remained same</td>
</tr>
<tr>
<td>Worsened</td>
</tr>
<tr>
<td>Total</td>
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</tbody>
</table>

**Macular thickness reduction**

The mean central macular thickness (OCT) at baseline was 615.7 ± 158.2 microns. Statistically significant reduction of macular thickness (P<0.001) was seen at 6 weeks 269 ± 105μ (mean improvement 346μ), at 3 months 262 ± 129μ (mean improvement 353μ), at 6 months 261 ± 142μ (mean improvement 348μ) and at final followup 273 ± 149 (mean improvement 342μ).

Overall there is a statistically significant difference in macular thickness (p<0.001) - Friedman Test

73.3 % patients had a central macular thickness (CMT) less than or equal to 250 microns at final followup visit.
Table 3 shows the macular thickness distribution among
the study group at final followup.

There was no direct correlation found between macular
thickness reduction and BCVA improvement, as macular
thickness reduction was more pronounced, preceded
BCVA improvement and due to the multiple factors
determining the latter. However, there was a general
trend of BCVA improvement associated with central
macular thickness (CMT) reduction, throughout the
study period (Figure 3).

Subgroup analysis was done to assess if early injection
was associated with better final visual outcome and
patients injected before 12 weeks since the onset of
CRVO (Gp 1) was compared with those injected after
12 weeks (Gp2) of disease onset. However, early
injection group was not found to be significantly
associated with better final BCVA improvement
(\(P= 0.557\)). (Table 4)

Subgroup analysis was done to assess if ischemic (Gp1)
and non ischemic (Gp2) nature of the disease has
impact on visual outcome. Ischemic CRVO was
significantly associated with poor final visual acuity
outcome (\(P= 0.026\)) (Table 5).

No ocular complications were noted during the entire
study period including glaucoma, cataract,
endophthalmitis, vitreous haemorrhage or retinal
detachment. However, a 55year old patient reported
an episode of ischemic heart disease 3 weeks following
his first injection. He was a hypertensive on treatment
with single drug and no other systemic diseases. It is
unsure if this was a coincidence or complication.

**Discussion**

Although the exact pathological sequence of CRVO is
unknown, visual acuity seems to be not only dependent
on macular ischemia, but mainly on CME and
photoreceptor damage in the early period of the disease.
The aim in RVO treatment should therefore include
different therapeutical aspects: (1) causal therapy for
improved blood circulation and (2) prevention of
secondary changes such as CME and neovascular
complications. Besides hemodilution \(^{2,3,4}\), additional
treatment options have been evaluated for the
improvement of blood circulation without conclusive
results so far.

With bevacizumab a new treatment option has been
introduced for early intervention against the formation

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**Table 3. Central macular thickness reduction in the study
group at final followup**

<table>
<thead>
<tr>
<th>Final CMT</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=250 microns</td>
<td>11</td>
<td>73.3</td>
</tr>
<tr>
<td>&gt;250 microns</td>
<td>4</td>
<td>26.7</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>100.0</td>
</tr>
</tbody>
</table>

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**Table 4. Duration of Disease vs final BCVA - (p. 0.557) - Mann - Whitney U Test**

<table>
<thead>
<tr>
<th>Duration of Disease</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks</td>
<td>Final BCVA (in logmar)</td>
<td>8</td>
<td>.00</td>
<td>2.00</td>
<td>.6500</td>
</tr>
<tr>
<td>12 weeks</td>
<td>Final BCVA (in logmar)</td>
<td>7</td>
<td>.00</td>
<td>1.17</td>
<td>.7243</td>
</tr>
</tbody>
</table>
of CME. Although the intravitreal injection of bevacizumab has already gained high clinical relevance for the treatment of retinal vascular diseases, to date only few short term studies have evaluated the course of CRVO after bevacizumab treatment. One retrospective study with 16 eyes found an improvement of visual acuity in 87.5% of the eyes treated after 3 months. A second retrospective study with 15 eyes found an increase in visual acuity of more than 3 lines in 40% of the patients treated. In a prospective study by Schaal et al with 6 months follow-up, 2.5 mg Bevacizumab was reported to improve visual acuity in 73.3% eyes with CRVO.

The present prospective case series of 15 patients with CRVO evaluates the 1 year course of visual acuity and central retinal thickness after bevacizumab injection. Peak VA was reached between 3 and 6 weeks after injection and ranged from 1 to 5 lines. Of the treated patients, 60% gained 3 or more lines. This number is in line with published data from retrospective and shorter term studies. 73.3% eyes resolved CME at final follow up and maximum reduction of macular thickness was achieved by 1-2 weeks following the injection. Central macular thickness reduction preceded improvement in BCVA. But, no direct correlation was found between VA and CMT reduction.

Both patients with low as well as high baseline VA benefited from bevacizumab injection. Patients with good initial visual acuity showed a tendency to gain 1-2 lines, whereas majority of patients with moderate visual loss (up to 6/60) gained more than 2 lines.

Stahl et al in their prospective study reported significantly better visual outcome in patients receiving bevacizumab within first 3 months of onset of CRVO compared to CRVO older than 4 months. However, in the present study and in a recent prospective study by Priglinger SG et al, no statistically significant difference in the final visual outcome was found between the early and late injection groups. This could be due to multiple factors influencing the visual outcome or a small sample size.

A subgroup analysis for different occlusion types revealed less visual acuity improvement for Ischemic CRVO patients compared to Non Ischaemic CRVO patients. Only 1 of the 4 eyes of Ischemic CRVO had 3 line improvement, mainly due to macular ischaemia or neovascular complications like vitreous haemorrhage. Three of the 4 ischaemic CRVO eyes developed neovascularization and 2 eyes with non ischemic CRVO had ischaemic conversion, while on treatment with Bevacizumab. Therefore, the current dose of 1.25 mg doesn't prevent neovascular complications in CRVO. Dose escalation studies like that of Costa et al with 2mg bevacizumab in Ischemic CRVO also has not shown improvement in the avascular or ischaemic status of the retina and further dose escalation studies are required to answer this issue. It must also be noted that due to the small patient number, subgroup analyses can only indicate tendencies and do not reflect statistically significant results.

The improvement of visual acuity after bevacizumab injection was concordant with a decrease in central retinal thickness. Regular OCT examinations can thus be regarded helpful for early detection of an impending drop in visual acuity after bevacizumab injection. An increase in central retinal thickness should be interpreted as an indication for re-injection. Regarding the number of re injections required to achieve a stable condition, this study showed a mean of 2.2 injections per patient (range 1-4 injections) during the study period. From the natural course of RVO, however, it is known that the imbalance between inflow and outflow of the retinal circulation can prevail for several months or even years. The formation of a new blood flow balance is presumably supported by the formation of collateral disc vessels with a new drainage route. It is likely that bevacizumab treatment must be upheld until a new balance between inflow and outflow in the retinal circulation is reached.

The main challenge in bevacizumab treatment is to maintain patients within the initially reached range of visual acuity by means of well-timed reinjections in...
combination with laser treatment for the treatment of secondary complications. Careful timing of bevacizumab injection and laser treatment for ischemic complications could have a beneficial effect.

The positive effect of bevacizumab injection on central retinal thickness and visual acuity is evident when mean values are considered, as was done in the present as well as other studies \(^{17,19,32}\). However, it should be emphasized that within our study population some individual treatment courses are not adequately reflected by the presentation of the mean values discussed above. Although most patients showed a good and reproducible response to bevacizumab treatment, a certain interindividual variability could be noted. In some patients, a decrease of central retinal thickness was accompanied by only a mild increase in visual acuity (due to macular ischemia, foveal haemorrhage with later RPE degeneration etc). In other patients, bevacizumab injection neither diminished central retinal thickness, nor improved visual acuity beyond week 3. These patients did not differ from the rest of the study population in terms of occlusion type, age of occlusion or patient age. It can only be assumed that the degrees of ischemia as well as other individual factors have an impact on treatment response.

The causes and mechanisms for treatment failure with bevacizumab injection have to be elucidated further in vitro as well as in clinical studies. The question whether bevacizumab might have negative long-term effects on collateral vessel formation due to its anti-VEGF action also needs to be addressed in these studies.

**Conclusion**

In summary, bevacizumab injection seems to improve the visual acuity in the majority of CRVO patients. This effect is probably due to a reduction of blood vessel permeability similar to the effect of intravitreally administered corticosteroids. In contrast to intravitreal corticosteroids, however, a rise in intraocular pressure was not observed in patients treated with intravitreal bevacizumab. In the present study, no other possible complications such as cataract, pseudo-endophthalmitis, endophthalmitis, central artery occlusion or retinal detachment were observed. We therefore suggest bevacizumab treatment for patients with CRVO under close postoperative observation. Around week 6 after bevacizumab treatment, re-injection should be considered based on the OCT and visual acuity findings, until the disease compensates.

**References**


Ocular Ischemic Syndrome (OIS): A Comparative Analysis of Management Options

Dr. Meena Chakrabarti MS, Dr. Valsa Stephen MS, Dr. Sonia Rani John DNB, Dr. Arup Chakrabarti MS

The term ocular ischemic syndrome (OIS) includes a constellation of ocular signs and symptoms secondary to severe, chronic arterial hypoperfusion to the eye and has been termed hypotensive retinopathy. The common causes for ocular hypoperfusion include 1) ipsilateral/bilateral carotid artery stenosis or occlusion 2) aortic arch syndrome 3) giant cell arteritis and 4) ophthalmic artery occlusion due to thromboembolism. This entity characteristically presents in individuals between 50-80 years of age and shows a significant male preponderance. Associated systemic diseases include systemic arterial hypertension (73 %), diabetes (56 %), ischemic heart disease (48 %), history of previous stroke (27 %) and deep vein thrombosis or thromboembolic episode. The classical triad of clinical findings for the diagnosis of OIS includes fundus finding of dilated nontortuous retinal vessels, mid peripheral dot and blot haemorrhages associated with anterior segment neovascularisation. The patient is symptomatic with visual loss in 70 %-90 % and ocular pain (dull aching or intractable pain) in 40 % of patients. Early recognition of this entity is absolutely essential as it may be the first manifestation of a carotid artery disease. The disease is relentlessly progressive and can lead to blindness (15 %), sudden cardiac deaths (63 %) or a debilitating stroke (19 %). A thorough systemic work up including the arm pulses, cardiology and neurological work up is essential. Estimation of ESR and CRP in all elderly patients will help rule out giant cell arteritis. Imaging studies such as Carotid Doppler Imaging, Magnetic Resonance Angiography may be necessary to confirm the diagnosis. Symptomatic patients with recurrent non-disabling strokes, hemispheric transient ischemic attacks and amaurosis fugax who has 70 %- 99% carotid artery stenosis will benefit from carotid endarterectomy. The 2 year ratio of stroke is reduced to 9 % in patients who have undergone this procedure from the 26 % incidence of stroke in patients who are on antiplatelets alone.

The treatment option for the ocular manifestation is limited to panretinal photocoagulation with causes regression of neovascularisation in 36 % of cases in early stages of the disease. As the diseases progress and as more and more of the angle gets occluded the success rate of PRP declines. Conservative management in the form of medical control of intraocular pressure, cyclodestructive procedures or glaucoma stents helps alleviate symptoms. There have been recent reports of the positive benefits of intravitreal injection of Triamcinolone acetonide in causing resolution of chronic cystoid macular oedema, and also on the use of intravitreal bevacizumab either singly or in combination with panretinal photocoagulation in causing regression of anterior segment neovascularisation and stabilizing the disease process.