Long-term effect of early intervention with single intravitreal injection of bevacizumab followed by panretinal and macular grid photocoagulation in central retinal vein occlusion (CRVO) with macular edema: A pilot study

NJ Shah and UN Shah

Abstract

Purpose To evaluate the effect of single-dose intravitreal bevacizumab followed by panretinal and macular grid laser, early in the course of central retinal vein occlusion (CRVO).

Methods It is a prospective, non-randomized, interventional study of nine eyes of nine patients with <10 days origin of CRVO who received 2.5 mg (0.1 ml) intravitreal bevacizumab, followed 3 weeks later by panretinal and macular grid photocoagulation. Its effect on visual acuity and anatomical features of CRVO were studied.

Results Nine eyes of nine patients (male:female = 8:1, mean age 54 years), with <10 days (average 2.67 days) onset of CRVO, received intravitreal bevacizumab within 7 days of presentation (average 3.1 days) followed 3 weeks later by panretinal with macular grid laser. Presenting mean baseline visual acuity was 20/320 (1.2 logarithm of the minimum angle of resolution (LOGMAR) units). All the patients showed rapid improvement in the form of rapid clearance of retinal hemorrhages, decreased optic disc swelling and venous dilation, and tortuosity. Mean final visual acuity was 20/63

(0.5 LOGMAR units). No patient showed conversion from non-ischemic to ischaemic CRVO, recurrence of macular edema, and disc collateral formation.

Conclusion Early intravitreal bevacizumab followed by panretinal and macular grid laser may provide visually and anatomically favourable results in a case of CRVO. It may also obviate the need for repeated injection. It requires a large randomized study to substantiate the results.

Eye (2011) 25, 239–244; doi:10.1038/eye.2010.225

Keywords: bevacizumab; central retinal vein occlusion; intravitreal injection; macular edema; panretinal photocoagulation; vascular endothelial growth factor

Introduction

Central retinal vein occlusion (CRVO), a common retinal vascular disorder, remains an important cause of painless visual loss in patients of age more than 50 years.¹ Macular edema is a common cause of visual loss in these patients. At this time, there is insufficient level I evidence to support any specific treatment to

The Eye Superspecialties,
Mumbai, India

Correspondence: NJ Shah,
The Eye Superspecialties
(TESS), An L V Prasad
Eye Institute Collaborating
Center, 201, Punit Plaza,
Next to Rajawadi Post office,
Ghatkopar (East), Mumbai,
400 077, India.
Tel: +91 440 222 516
7070; Fax: +91 440 222
516 7071.
E-mail: urminikunj@
hotmail.com

Received: 18 October 2010
Accepted in revised form:
21 December 2010

improve vision in CRVO.² However, a variety of interventions are available such as systemic anticoagulation, panretinal photocoagulation (PRP), macular grid photocoagulation, hemodilution, laser chorioretinal venous anastomosis and radial optic neurotomy/laminar puncture, and so on.

Intravitreal levels of vascular endothelial growth factor (VEGF) in CRVO are the highest of those measured in retinal vascular disease.³ Various studies have confirmed that intravitreal injection of bevacizumab (a pan VEGF blocker) improves the visual acuity in these patients by virtue of reduction in macular edema and reversal of fundus changes.⁴⁻⁷

Bevacizumab treatment early after the onset of CRVO was associated with statistically significant reduction in venous dilation, tortuosity, optic disc swelling and macular edema, and a dramatic improvement in visual acuity.^{8,9} However, need of repeated injections at regular intervals to maintain the visual gain has been a major drawback. Although, central retinal vein occlusion study (CVOS) showed benefit of PRP for proliferative stage of CRVO, iris neovascularisation developed less frequently in prophylactically treated eyes as compared with untreated eyes, although statistically insignificant.¹⁰ Also, in CVOS although macular grid photocoagulation did not lead to significant improvement in visual acuity it significantly decreased angiographic macular edema at 12 month follow-up.¹¹ Thus suggesting that retinal photocoagulation has a stabilizing role to play.

In this study, we combined the beneficial effect of early treatment with intravitreal bevacizumab and the stabilizing effect of laser to treat our patients in an attempt to obviate the need for repeated intravitreal injections.

Materials and methods

It was a prospective non-randomized clinical interventional study of nine eyes of nine consecutive patients with recent onset clinically diagnosed and angiographically proven CRVO with macular edema.

The patients were informed about the experimental nature of the treatment and had to sign an informed written consent form.

All patients of CRVO with macular edema and decreased visual acuity irrespective of degree of ischaemia were included in the study. Patients with more than 1 month duration of onset, history of previous treatment for CRVO, other retinal disease, such as diabetic retinopathy likely to affect visual acuity and less than 1 year follow-up, were excluded.

At presentation, patients underwent complete ophthalmic evaluation, which included Snellen's visual

acuity assessment, slit-lamp biomicroscopy and indirect ophthalmoscopy. Digital fundus fluorescein angiography (FFA, Carl Zeiss Meditec AG, Jena, Germany) was done to confirm the diagnosis, classify the type of CRVO (according to the CRVO study criteria), and evaluate the presence of macular edema.

All the patients were treated with 2.5 mg (0.1 ml) of intravitreal injection of bevacizumab (Genentech, San Diego, CA, USA) on presentation. The injection was performed in the operation theatre under strict aseptic precautions.

The patients were examined on day 1, day 7, and 3 weeks postoperatively. At each visit routine evaluations, which included Snellen's best corrected visual acuity (BCVA), intraocular pressure measurement by applanation tonometry, slit-lamp biomicroscopy and indirect ophthalmoscopy, were done. The visual acuity measurements were converted to logarithm of the minimum angle of resolution (LOGMAR).

Panretinal laser photocoagulation with macular grid laser, (average 3600 shots over three sittings with 200–300 mW power, 200–300- μ spot size for panretinal laser and 100 mW power with 50- μ spot size for macular grid laser) was performed in all patients starting at 3 weeks after the injection, over three sittings, on alternate days in all cases.

Thereafter, all the patients were followed up on a monthly basis for 6 months and later on a 3-month basis for 1 year, or last follow-up visit whichever was later. Besides routine evaluation, FFA was to be done at each such visit if there was clinical suspicion of recurrence of macular edema or to detect any neovascular complication in the event of conversion from non-ischemic to ischaemic CRVO.

Main outcome measures included improvement in visual acuity and fundus appearance. Conversion from non-ischemic to ischaemic CRVO, recurrence of macular edema, disc collateral formation, and need for repeat injections were also studied.

Results

It was a prospective study of nine eyes of nine patients with CRVO. Four out of nine (44.44%) eyes had non-ischemic CRVO, 5/9 (55.55%) eyes had ischaemic CRVO. Overall, 8/9 (88.88%) patients were males and only 1/9 (11.11%) patients was female, with age ranging from 42 to 70 years (mean age 54 years). Among the systemic predisposing factors, hypertension alone was present in 4/9 patients (44.44%), pulmonary thromboembolism in 1/9 patients (11.11%) and hyperhomocysteinemia in 2/9 patients (22.22%). Whereas hypertension combined with diabetes was present in 1/9 (11.11%) and with hyperhomocysteinemia

in 1/9 (11.11%) patients. All patients presented within 10 days of onset of symptoms (average 2.67 days).

Presenting BCVA was $<20/200$ in 5/9 (55.55%) and 20/50 to 20/200 in 4/9 (44.44%) eyes. All patients were treated with intravitreal bevacizumab within <7 days of presentation (average 3.1 days). Postoperatively, none of the patients had any local or systemic side effects of injection such as endophthalmitis, clinically evident inflammation, retinal tears, retinal detachment, or thromboembolic events. Conjunctival hyperaemia was present in all and subconjunctival hemorrhage in 3/9 (33.33%) eyes.

All the patients showed rapid improvement in the form of rapid clearance of retinal hemorrhages, decreased optic disc swelling and decreased venous dilation, and tortuosity. This was clinically evident as early as at the 7 day after injection follow-up in all the patients. Figure 1a shows fluorescein angiogram on presentation in one of the study patients with CRVO showing severe dilation and tortuosity of venous circulation, blocked fluorescence due to superficial retinal hemorrhages, disc hyperfluorescence and macular leakage; Figure 1b shows the post treatment fluorescein angiogram in the same patient with complete resolution of macular edema. Scars of laser photocoagulation are seen.

Final post-operative vision was $<20/200$ in 2/9 (22.22%) eyes and $>20/40$ in 7/9 (77.78%) eyes. Mean baseline visual acuity (VA) improved from 20/320 (LOGMAR units, 1.2) to 20/63 (LOGMAR units, 0.5) at the final follow-up visit. (Figure 2 shows the plot of change in BCVA against time in all patients, till the last follow-up visit and Table 1 shows summary of patient data).

Discussion

CRVO, a common retinal vascular disorder, remains an important cause of painless visual loss in patients more than 50 years of age.¹ The clinical appearance typically demonstrates four quadrants of intraretinal hemorrhages with dilated and tortuous retinal veins. Macular edema, optic disc edema, and cotton-wool spots may be present to a variable degree. CRVO is broadly divided into two clinical subtypes, based on the degree of ischaemia: non-ischemic CRVO is typically associated with relatively better vision and a better prognosis for spontaneous visual improvement; ischaemic CRVO is typically associated with more profound visual loss on presentation, a relative afferent pupillary defect, and a relatively higher risk for neovascular glaucoma.

The most common cause of visual loss in patients with CRVO is macular edema. Other causes of visual loss include macular ischaemia and neovascular glaucoma.

Figure 1 (a) Shows fluorescein angiogram on presentation in one of the study patient with CRVO showing severe dilation and tortuosity of venous circulation, blocked fluorescence due to superficial retinal hemorrhages, disc hyperfluorescence, and macular leakage; (b) shows Post-treatment fluorescein angiogram in the same patient with complete resolution of macular edema. Scars of laser photocoagulation are seen.

Figure 2 Graph shows the plot of change in best corrected visual acuity (Log MAR) against time in all patients.

Table 1 Summary of patient data

Age	Sex	CRVO type	DOP (days)	DPT (days)	Systemic disease	Pre op VA	LOG MAR VA	VA range	Post op VA	LOG MAR VA	VA range	Follow-up (months)	Fundus appearance		Conversion from I to NI CRVO	Recurrent macular edema	Disc collateral	Repeat injection
													First sign of resolution (days)	Complete resolution (weeks)				
65	M	NI	1	2	H	20/80	0.6	20/50-20/200	20/30	0.2	≥20/40	24	7	3	N	N	N	N
45	M	NI	10	2	HT, DM	20/80	0.6	20/50-20/200	20/30	0.2	≥20/40	24	7	3	N	N	N	N
61	M	I	1	4	PT	20/1200	1.8	<20/200	20/1200	1.8	<20/200	18	7	3	N	N	N	N
52	M	NI	2	3	H	20/80	0.6	20/50-20/200	20/30	0.2	≥20/40	24	7	3	N	N	N	N
45	M	NI	3	2	HT	20/60	0.5	20/50-20/200	20/25	0.1	≥20/40	18	7	3	N	N	N	N
70	M	I	2	2	HT	20/2000	2	<20/200	20/400	1.3	<20/200	24	7	3	N	N	N	N
56	M	I	2	4	HT	20/1000	1.7	<20/200	20/40	0.3	≥20/40	24	7	3	N	N	N	N
50	M	I	2	2	HT, H	20/1600	1.9	<20/200	20/40	0.3	≥20/40	18	7	3	N	N	N	N
42	F	I	1	7	HT	20/1000	1.7	<20/200	20/30	0.2	≥20/40	18	7	3	N	N	N	N

Key: DM, diabetes mellitus; DOP, duration from onset to presentation; DPT, duration from presentation to treatment; E, female; H, hyperhomocysteinemia; HT, hypertension; I, ischemic; M, male; N, no; NI, non-ischemic; Post op, postoperative; Pre op, preoperative; PT, pulmonary thromboembolism; VA, visual acuity.

A variety of interventions have been implicated to improve vision in CRVO.² Especially, the off-label use of intravitreal injection of bevacizumab for macular edema has been studied extensively.⁴⁻⁷

Bevacizumab is a full-length recombinant humanized antibody, active against VEGF, and approved for use in colorectal cancer.¹² Off-label intravitreal injection of bevacizumab was first reported as a potential therapy for macular edema secondary to CRVO in 2005.¹³ In several case series, bevacizumab was reported to improve macular edema associated with CRVO, at least in the short term.⁴⁻⁷ Patients experienced a dramatic improvement in the visual acuity and clinical fundus appearance, without collateral vessel formation.⁹

In addition, bevacizumab appears to have activity against anterior segment neovascularization. This approach is used most often in cases of non-ischemic CRVO, but bevacizumab may be effective to treat complications of ischaemic CRVO as well. The visual benefits of intravitreal bevacizumab for macular edema due to CRVO are apparent early but are not sustained without need for repeated injections. A larger clinical study and long-term follow-up will be necessary to better elicit the best regimen for this therapy.¹⁴

CVOS was a randomized clinical trial wherein eyes with at least 10 disc areas of retinal capillary non-perfusion, prophylactic scatter photocoagulation did not prevent the development of anterior segment neovascularization. The CVOS concluded that it was safe to observe these eyes until early neovascularization of the iris or angle developed. Neovascularization regressed after treatment in 56% of photocoagulation-naïve eyes and 22% of eyes treated previously with scatter photocoagulation.¹⁰

Iris neovascularisation developed less frequently in prophylactically treated eyes as compared with untreated eyes, although statistically insignificant. Iris or angle neovascularisation developed in 117/714 (16%) of eyes. A total of 61/117 (52%) eyes that had iris or angle neovascularisation were initially categorized as perfused.¹⁵ Also one-third patients with non-ischemic CRVO converted into ischaemic CRVO. On this basis, all our patients received prophylactic PRP.

Recurrent macular edema may occur in patients with CRVO following treatment with bevacizumab; in some cases, the recurrent macular edema may be more severe than the pretreatment macular edema ('rebound' macular edema).¹⁶ Macular grid laser was given to all our patients to counter macula edema, which was the main cause of vision loss, and also the reason for reappearance of macular edema was the main indication for requirement of repeated injections. In CVOS, eyes with perfused macular edema on FFA and a visual acuity of 20/50 or worse were randomized to treatment with macular grid laser photocoagulation or observation only

(no treatment). Although macular grid photocoagulation did not lead to statistically significant improvement in visual acuity, it significantly decreased angiographic macular edema. At the 12 month follow-up evaluation, all 72 untreated eyes (100%) had persistent angiographic leakage while 21/68 (31%) treated eyes had no quantifiable leakage ($P < 0.0001$).¹¹ In younger individuals, grid laser was suggested to be value in achieving better visual outcome. Our study patients were relatively younger with mean age of 54 years.

We combined the beneficial effect of intravitreal bevacizumab for vision gain with the stabilizing effect of laser to maintain the gain. Although, prophylactic PRP and macular grid photocoagulation did not show any statistically significant benefit in CRVO study, we included it in our protocol owing to its vision-stabilizing role especially to compensate for the short lasting effect of bevacizumab in the hope to reduce re-treatments for recurrent macular edema and to prevent neovascular complications.

According to CVOS, the BCVA at presentation was demonstrated to serve as an indicator of the final visual outcome.¹⁵ Although there is a vast difference between the sample size of CVOS and current study, a comparison of final visual outcome is notable. Among 209/714 eyes with the presenting BCVA of $>20/40$, 136 (65%) retained the vision, 52 (25%) deteriorated to 20/50 to 20/200, and 21 (10%) attained $<20/200$ BCVA. However, none of our patients had a presenting visual acuity $>20/40$.

In CVOS, of the 304/714 eyes with presenting BCVA of 20/50 to 20/200 58 (19%) eyes improved to $>20/40$, 133 (44%) eyes remained stable, and deterioration to $<20/200$ BCVA was seen in 113 (37%) eyes. In our study, all (100%) patients in this group improved and attained $>20/40$ BCVA.

In CVOS, of the 201/714 eyes with presenting BCVA $<20/200$ (most eyes), 564 (79%) eyes retained poor visual acuity, 39 (19%) eyes improved to 20/50 to 20/200 and only three (1%) eyes improved to $>20/40$. In our study, 3/5 (60%) developed $>20/40$ visual acuity and 2/5 (20%) patients remained at $<20/200$.

Mean baseline VA improved from 20/320 (LOGMAR units, 1.2) to 20/63 (LOGMAR units, 0.5) at the final follow-up visit. This was comparable or better than the results of other early intervention studies.^{8,9}

Although visual acuity did not improve significantly in all our patients, a significant reversal of anatomical features of CRVO was seen in all the patients. This suggests that besides the anti-permeability property of bevacizumab there exists an unknown mechanism, within the retinal venous system other than the thrombus, to be inhibited by bevacizumab.⁹

Collaterals are alternate pathways of venous outflow to compensate for poor venous outflow through the

central vein. Collateral vessels at the optic nerve were seen to develop in $\sim 77\%$ of CRVO cases in a study by Takahashi *et al.*¹⁷ None of our patient had visible collateral formation. Absence of collaterals in these patients implies that the treatment must have led to an improvement in the venous flow.⁹

In CVOS, at final follow-up visit, 34% of eyes showed conversion of non-ischemic to ischaemic CRVO.¹⁵ However, in our study none of the patients showed conversion.

This series, although prospective, has many drawbacks. The sample size was small. This was because it was a pilot study, also as the nature of treatment was prophylactic there was limited patient enrolment and it was a single center study. There was a lack of control group and masking of investigators and patients. Optical coherence tomography (OCT) was not done due to non-availability. However, FFA could not be deemed as ineffective for monitoring of macular edema, but for its invasive nature. The classification of patients into non-ischemic and ischaemic CRVO on the basis of FFA may be less reliable as in the acute stage extensive fundus hemorrhages may mask the actual areas of non-perfusion.

However, these drawbacks cannot undermine the results of this study especially when the early natural history of the disease that is, within 3 months has seldom being studied in detail. It suggests that early treatment with bevacizumab may have twofold effects in the form of early reversal of venous tortuosity and macular edema. Second, it improves the flow assuming that it inhibits VEGF which is known to cause decrease venous flow and retinal perfusion.^{8,9}

There are many salient features of this study. It includes early treatment of patients (within 10 days of presentation); the aim was to limit the irreversible damage by early intervention, no collateral formation, and better visual outcome compared with natural course. Most striking finding of the study was lack of necessity to re-inject bevacizumab. It also suggests a stabilizing role for PRP in an eye previously treated with an anti-VEGF agent. As there is no comparative study, the reason behind this cannot be ascertained. However, we propose that it would have had a sustained effect on the VEGF suppression induced by bevacizumab. It could have also prevented conversion of non-ischemic to ischaemic CRVO, occurrence of neovascular complications, and recurrence of macular edema.

In conclusion, the results of the present study suggests that early treatment with intravitreal bevacizumab followed by PRP may provide visually and anatomically favourable results in a case of CRVO and also obviate the need for repeated injection. This however, requires a randomized study with large sample size to substantiate the results.

Summary

What was known before

- Central retinal vein occlusion (CRVO), a common retinal vascular disorder, remains an important cause of painless visual loss in patients of age more than 50 years. Macular edema is a common cause of visual loss in these patients. At this time, there is insufficient level I evidence to support any specific treatment to improve vision in CRVO. However, a variety of interventions are available viz. systemic anticoagulation, pan retinal photocoagulation (PRP), macular grid photocoagulation, hemodilution, laser chorioretinal venous anastomosis and radial optic neurotomy/laminar puncture, and so on. Intravitreal levels of vascular endothelial growth factor (VEGF) levels in CRVO are the highest of those measured in retinal vascular disease. Various studies have confirmed that intravitreal injection of bevacizumab (a pan VEGF blocker) improves the visual acuity in these patients by virtue of reduction in macular edema and reversal of fundus changes.

What this study adds

- Treatment with intravitreal Bevacizumab early in the course of central retinal vein occlusion followed by pan retinal and macular grid photocoagulation may provide visually and anatomically favorable results. It may obviate the need for repeated injections and prevent neovascular complications.

Conflict of interest

The authors declare no conflict of interest.

References

- Gutman FA. Evaluation of a patient with central retinal vein occlusion. *Ophthalmology* 1990; **90**: 481–483.
- Mohamed Q, McIntosh RL, Saw SM, Wong TY. Interventions for central retinal vein occlusion: an evidence-based systematic review. *Ophthalmology* 2007; **114**: 507–519, 524.
- Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST *et al*. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med* 1994; **331**: 1480–1487.
- Iturralde D, Spaide RF, Meyerle CB, Klancnik JM, Yannuzzi LA, Fisher YL *et al*. Intravitreal bevacizumab (Avastin) treatment of macular edema in central retinal vein occlusion: a short-term study. *Retina* 2006; **26**: 279–284.
- Pai SA, Shetty R, Vijayan PB, Venkatasubramaniam G, Yadav NK, Shetty BK *et al*. Clinical, anatomic and electrophysiologic evaluation following intravitreal bevacizumab for macular edema in retinal vein occlusion. *Am J Ophthalmol* 2007; **143**: 601–606.
- Spandau UH, Ihloff AK, Jonas JB. Intravitreal bevacizumab treatment of macular edema due to central retinal vein occlusion. *Acta Ophthalmol Scand* 2006; **84**: 555–556.
- Stahl A, Agostini H, Hansen LL, Feltgen N. Bevacizumab in retinal vein occlusion-results of a prospective case series. *Graefes Arch Clin Exp Ophthalmol* 2007; **245**: 1429–1436.
- Rensch F, Jonas JB, Spandau UH. Early intravitreal bevacizumab for non-ischemic central retinal vein occlusion. *Acta Ophthalmologica* 2009; **87**: 77–81.
- Ferrara DC, Koizumi H, Spaide RF. Early bevacizumab treatment of central retinal vein occlusion. *Am J Ophthalmol* 2007; **144**: 864–871.
- The Central Vein Occlusion Study Group. A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion: The Central Vein occlusion Study Group N report. *Ophthalmology* 1995; **102**: 1434–1444.
- The Central Vein Occlusion Study Group. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion: the Central Vein Occlusion Study Group M report. *Ophthalmology* 1995; **102**: 1425–1433.
- Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W *et al*. Bevacizumab plus irinotecan, fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350**: 2335–2342.
- Rosenfeld PJ, Fung AE, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for macular edema from central retinal vein occlusion. *Ophthalmic Surg Lasers Imaging* 2005; **36**: 336–339.
- Kaiser RS, Sivalingam A, Abraham P, Abraham P, Fineman MS, Samuel MA *et al*. Intravitreal bevacizumab (avastin) in central retinal vein occlusion. *Retina* 2007; **27**: 1013–1019.
- The Central Vein Occlusion Study Group. Natural history and clinical management of Central Retinal vein Occlusion. *Arch Ophthalmol* 1997; **115**: 486–491.
- Matsumoto Y, Freund KB, Peiretti E, Cooney MJ, Ferrara DC, Yannuzzi LA. Rebound macular edema following bevacizumab (Avastin) therapy for retinal venous occlusive disease. *Retina* 2007; **27**: 426–431.
- Takahashi K, Muraoka K, Kishi S, Shimizu K. Formation of retinochoroidal collaterals in central retinal vein occlusion. *Am J Ophthalmol* 1998; **126**: 91–99.