



King Saud University
Saudi Journal of Ophthalmology

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**ORIGINAL ARTICLE**

Early Avastin management in acute retinal vein occlusion

Shaaban A. Mehany, MD *, **Khaled M. Mourad, MD**, **Ahmad M. Shawkat, MD**,
Mohammed F. Sayed, MD

Department of Ophthalmology, El-Minia Faculty of Medicine, El-Minia University Hospitals, El-Minia University, Egypt

Received 20 March 2010; accepted 20 March 2010

Available online 4 April 2010

KEYWORDS

Retinal venous occlusion;
Avastin (bevacizumab)
CRVO;
BRVO;
FA and OCT;
Intravitreal injection

Abstract *Purpose:* To evaluate the safety, functional and anatomical effects of intravitreal Avastin (bevacizumab) in treatment of recent retinal venous occlusion.

Design: Prospective interventional series non-comparative study.

Setting: Department of Ophthalmology, Faculty of Medicine, El-Minia University, Egypt.

Methods: The study included 30 eyes of 30 patients with recent retinal venous occlusion of less than 3 months duration 12 eyes (40%) of patients with central retinal vein occlusion (CRVO) and 18 eyes (60%) with branch retinal vein occlusion (BRVO) were injected with intravitreal bevacizumab 1.25 mg (0.05 ml) of commercially available bevacizumab [Avastin; Genentech, Inc., San Francisco, CA] at a concentration of 25 mg/ml as a primary treatment. The mean number of injections was 2.7 (range, 1–6 injections) 6–8 weeks intervals and follow-up for 12 months (range, 9–13 months). Patients underwent visual acuity testing (VA) as functional assessment. Anatomically, optical coherence tomography (OCT) is used for measurement of central retinal thickness (CRT) to detect macular edema (ME), fundus photography and fluorescein angiography (FA) to detect venous tortuosity, optic disc edema and surface wrinkling rather than ME. All finding at baseline and each follow-up visit were reported.

Results: The mean age of all patients was 65.3 years \pm 8.5 (range, 55–82 years), 20 males and 10 females patients. The mean baseline VA was 20/240 (log MAR 1.08 \pm 0.52) and improved to 20/

* Corresponding author. Address: Dr. Abdulrahman Al-Mishary Hospital, P.O. Box 56929, Riyadh 11564, Saudi Arabia. Tel.: +966 01 4657700x1244; fax: +966 01 4625040.
E-mail address: shaabanhamid@yahoo.com (S.A. Mehany).



60 (log MAR 0.48 ± 0.32) with statistically significance difference change ($P < 0.001$). The mean baseline CRT was $455 \mu\text{m} \pm 126$ (range, 386–510), decreased to $356 \mu\text{m} \pm 118$ (range, 296–416) after 1 month with statistically significance difference change ($P < 0.02$) and to $402 \mu\text{m} \pm 170$ (range, 338–468) after 6 months ($P < 0.067$) and to $250 \mu\text{m} \pm 48$ (range, 200–298) at last follow-up with statistically significance difference change from the baseline ($P < 0.001$). There were great proportional decrease in venous tortuosity, optic disc edema and surface wrinkling after 1 month of injection. Neither systemic nor intraocular adverse events were reported.

Conclusions: Intravitreal Avastin (IVA) is safe well tolerated, effectively improve VA, fundus picture and stabilize anterior segment neo-vascular activity in patients with recent retinal venous occlusion.

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1. Introduction

Retinal vein occlusions (RVOs) disease is not uncommon and remains the second most common sight-threatening vascular disorder following diabetic retinopathy (Central Vein Occlusion Study Group, 1997). The incidence of CRVO is currently reported as 1.8% (Klein et al., 2008). The treatment of macular edema in this condition remains challenging and controversial. At the present time, the therapeutic efforts for sustained functional improvement remain limited. Despite concerted efforts to treat patients both medically and surgically, no clear consensus on a treatment modality or guidelines have emerged since the branch vein occlusion (BVO) and central vein occlusion (CVO) studies (Alexander and Netan, 2008). RVOs cause decreased tissue perfusion and increased hydrostatic pressure within the involved segments as a consequence of vascular obstruction. This leads to a constellation of findings including intraretinal hemorrhages, exudation of fluid and varying levels of ischemia, surface wrinkling retinopathy, and possible development of neo-vascular complications (Hayreh, 1983).

Several therapeutic methods are used to treat the macular edema secondary to BRVO (Rehak and Rehak, 2008; Hoerauf, 2007; McIntosh et al., 2007). Although macular grid laser photocoagulation was initially recommended based on the results of the (BVOS) (The Branch Vein Occlusion Study Group, 1984). Later studies suggested that the improvement of visual function by this treatment was limited (Battaglia et al., 1999a,b). Unfortunately, the CVOS showed no benefit of macular grid laser treatment on CME due to CRVO. Accordingly, investigators have looked at other approaches to treat CME due to BRVO and CRVO, including laser-induced chorioretinal anastomosis, radial optic neurotomy, arteriovenous sheathotomy, intravitreal tissue plasminogen activator and therapy with intravitreal steroids or anti-vascular endothelial growth factor (VEGF) agents such as Pegaptanib sodium (Macugen, Eyetech/Pfizer), Ranibizumab (Lucentis, Genentech), or bevacizumab (Avastin, Genentech). Intravitreal injection of corticosteroids (triacinolone acetate) has been reported to be effective for the macular edema secondary to RVOs (Jonas et al., 2005; Avitabile et al., 2005). However, this therapy is often associated with cataract formation and elevation of intraocular pressure especially if repeated injections are required (Ozkiris et al., 2006; Cekic et al., 2005).

The results of recent studies (Noma et al., 2008, 2006) have shown that the level of vasopermeability factors, including vascular endothelial growth factor, was significantly increased in the vitreous of patients with RVOs. In addition, it has been shown that an intravitreal injection of bevacizumab (Avastin,

Genentech, Inc., San Francisco, CA), a full-length recombinant monoclonal antibody against human vascular endothelial growth factor (VEGF), is effective in reducing the macular edema that develops in eyes with RVOs (Kreutzer et al., 2008; Chung et al., 2008; Kriechbaum et al., 2008; Wu et al., 2008; Spandau et al., 2007; Rabena et al., 2007; Costa et al., 2004). Thus, the inhibition of vascular endothelial growth factor by bevacizumab injection has become an alternative treatment for the macular edema secondary to RVOs. A favorable short term studies to intravitreal Avastin (IVA) injection suggest a possible role of VEGF in RVOs. However, there are very few reports on the long-term results of this treatment (Jaisse et al., 2009; Prager et al., 2009).

The purposes of this study were to evaluate the results of 12 months after intravitreal bevacizumab therapy regarding to safety, functional and anatomical effects in treatment of recent retinal venous occlusions.

2. Patients and methods

This prospective interventional series non-comparative study included 30 eyes of 30 patients with recent RVOs (less than 3 months in duration). Twelve eyes (40%) had CRVO and 18 (60%) had BRVO. All patients fulfilled the following inclusion criteria: recent onset with no previous treatment for RVO, non-ischemic type (less than 10 disc diameter of non-perfusion in CRVO and less than 5 disc diameter of non-perfusion in BRVO). All patients had baseline clinical examinations, which included a Snellen visual acuity test, intraocular pressure measurement using applanation tonometry, slit lamp examination of the anterior segment, fundus biomicroscopy with Volk 90 and 78 diopters lenses, dilated fundus examination with indirect ophthalmoscopy and fundus photography and fluorescein angiography. Optical coherence tomography (OCT) was performed for all of patients. Stratus OCT3 (Carl Zeiss Meditec, Dublin, CA) was performed. Readings for 1 mm central retinal thickness (CRT) were obtained from the mean retinal thickness in the central subfield using six linear scans 6 mm long centered on fixation and processed as a retinal map.

In all patients, the intravitreal injection of off label bevacizumab was performed in a standard protocol in the operating theater under operating ophthalmoscope and complete aseptic condition after obtaining informed consent. Topical 0.4% benoxinate hydrochloride was applied to the ocular surface followed by scrubbing of the eye lids and lashes with 10% of povidone iodine and conjunctiva installed with 5% povidone iodine three times several minutes apart. A sterile eyelid speculum was used for all injections, sub-conjunctival 1 cc

lidocaine 2% was done at the site of bevacizumab injection in the inferotemporal quadrant. Bevacizumab was injected through the pars plana 3.5–4.0 mm posterior to the surgical limbus using a 30-gauge needle at a dose of 1.25 mg in 0.05 ml. Post-injection, a sterile cotton swab is placed at the site of injection to prevent reflux of vitreous or drug, light perception was assessed and indirect ophthalmoscope to see optic nerve head perfusion. The intraocular pressure (IOP) was monitored until it decreased below 30 mm Hg if it is elevated after injection.

After the injection, the patients were instructed to apply topical antibiotics to the injected eye four times a day for 5 days. Postoperative follow-up included repeated clinical examinations and OCT to all of the patients. Patients were assessed for adverse events including elevated intraocular pressure, cataract progression, retinal detachment, post-injection inflammation, and endophthalmitis. Follow-up evaluations were scheduled to next day, 1 week then monthly till the end of follow-up. A repeated injection of bevacizumab was performed for persistent or recurrent macular edema (ME) seen by fluorescein angiography documented by OCT and clinically drop of visual acuity measurements.

Treatment success was evaluated by either CRT of $\leq 260 \mu\text{m}$ or best corrected visual acuity (BCVA) of 20/40 (0.30 log MAR) or better, those patients no further injection were needed. Borderline improvement (\downarrow in CMT by at least $50 \mu\text{m}$ from the baseline OCT measurement) and non-improved patients with persistent or recurrent macular edema were scheduled for further injections.

Statistical analysis was assessed using (SPSS, version 13, SPSS, Inc., Chicago, Illinois, USA). All variables were expressed as mean \pm standard deviation (SD), the paired Student *t*-test was used and *P* value ≤ 0.05 was considered statistically significant. Snellen's BCVA measurements were converted to logarithmic minimal angle resolution (log MAR) equivalents to perform the statistical analysis. Main outcome measures changes in BCVA and CMT, secondary outcome are the adverse effects and the need for re-injection.

3. Results

Thirty eyes of 30 patients received intravitreal Avastin (IVA) injection in this study. Out of them 12 eyes (40%) with central retinal vein occlusion (CRVO) (Fig. 1) and 18 eyes (60%) with branch retinal vein occlusion (BRVO) (Figs. 2–5). The mean age of all patients was $65.3 \text{ years} \pm 8.5$ (range, 55–82 years), 20 males and 10 females patients. All of patients were of non-ischemic type with recent retinal venous occlusion less than 3 months (range, 1 day to 3 months). Follow-up period was 12 months (range, 9–13 months). At the baseline OCT demonstrate increasing in the 1-mm central retinal thickness (CRT) in all of the studied eyes in which the mean CRT was $455 \pm 126 \mu\text{m}$ (range, 386–510) due to marked macular edema, often with cystoid spaces seen clinically as well as documented by OCT, decreased to a mean of $280 \pm 72 \mu\text{m}$ (range, 240–340) after 1 week of injection with a difference of $175 \mu\text{m}$ from the baseline and this is highly significant difference ($P < 0.01$) (Table 1, Fig. 6).

The mean CRT increased again to $356 \pm 118 \mu\text{m}$ (range, 296–416) after 1 month of injection with a difference of $99 \mu\text{m}$ from the baseline and still significantly different ($P < 0.02$). At 3 months the mean CRT decreased again to $302 \pm 86 \mu\text{m}$ (range, 270–368) with a difference of $153 \mu\text{m}$ from the baseline and still significantly different ($P < 0.01$). The marked increasing again of the mean CRT on the follow-up period was seen at 6 months in which it was $402 \pm 170 \mu\text{m}$ (range, 338–468) with the little difference from mean baseline which was $53 \mu\text{m}$ difference due recurrence of macular edema, and it was not significant from the baseline ($P < 0.067$). At 12 months the mean CRT decreased to lowest level which it was $250 \pm 48 \mu\text{m}$ (range, 200–298) with the highest significantly difference from the mean baseline, in which the difference was highest, $205 \mu\text{m}$ ($P < 0.001$) (Table 1, Fig. 6).

The mean best corrected visual acuity (BCVA) revealed significant improvement at all time points compared with baseline and continued to improve all over the study with repeated injections (Table 1, Fig. 7). At baseline the mean BCVA was

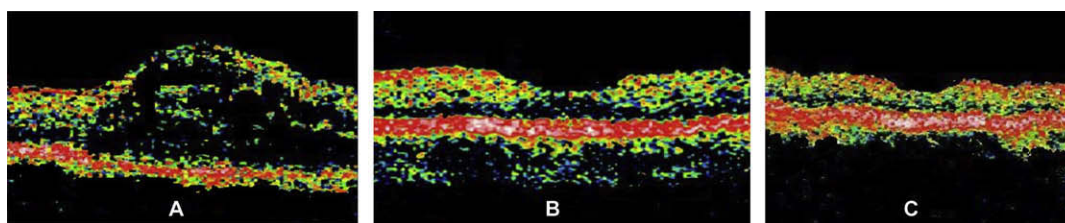


Figure 1 (A) OCT of a case of CRVO at baseline with \uparrow CRT and sponge like CME; (B) OCT of the same case after 3 (IVA) injections with marked resolution of CME; (C) OCT of the same case at the end of follow-up (successful treatment).

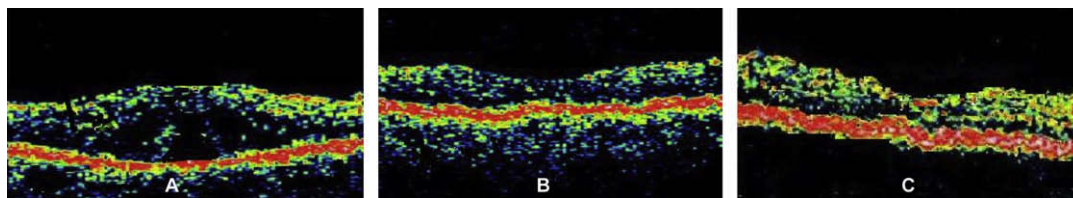


Figure 2 (A) OCT of a case of superior temporal BRVO at baseline with CME; (B) OCT of the same case after two IVA injections (6 months); (C) OCT of the same case at the end of follow-up (successful treatment).

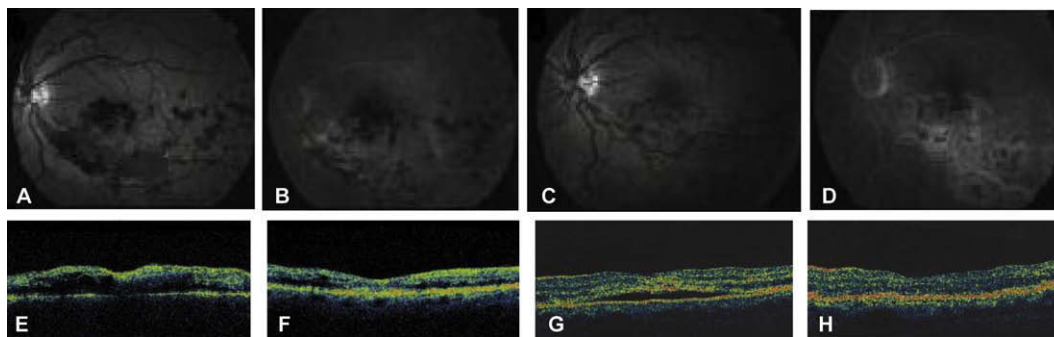


Figure 3 (A) Lt., inferior temporal BRVO, red free fundus photography; (B) Lt., inferior temporal BRVO, FA showing Fl. dye leakage of ME; (C) Lt., inferior temporal BRVO, red free same case 6 months after IVA injection; (D) Lt., inferior temporal BRVO, FA, same case 6 months after IVA injection; (E) OCT, of the same case at baseline showing \uparrow CMT due to CME; (F) OCT, with initial resolution of CME and \downarrow CMT 1 week of IVA injection; (G) OCT showing recurrence of CME 6 months after first injection; (H) OCT of the same case at the end of follow-up with successful resolution of CME.

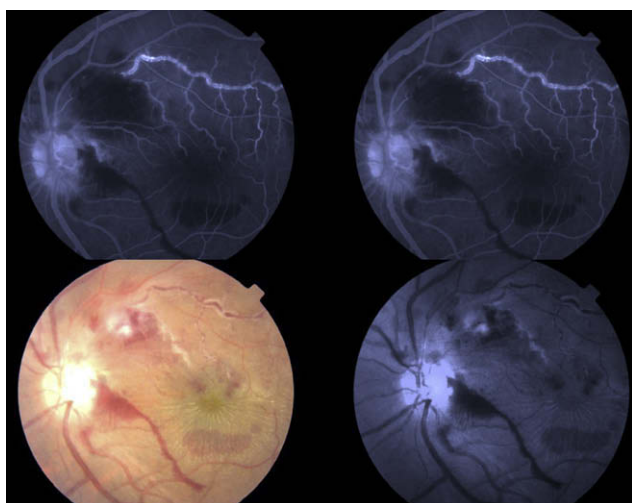


Figure 4 (A) Fundus photography and FA of a case of Lt., superior macular BRVO showing retinal Hge, cotton wool spots, exudates and surface wrinkling maculopathy seen next day of occlusion.

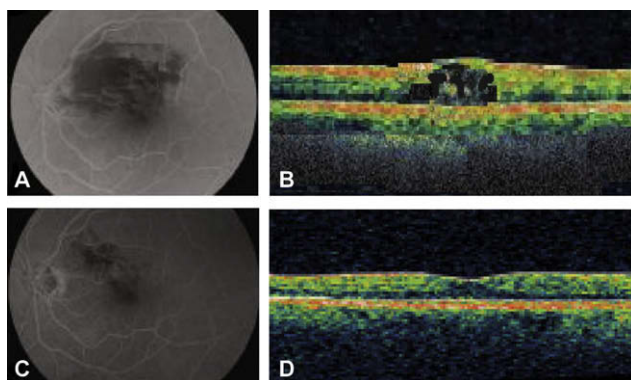


Figure 5 (A) FA, of Lt., upper temporal BRVO at baseline; (B) OCT of the same case with ME and \uparrow CRT at baseline; (C) FA, of the same case 1 month after first IVA injection (\downarrow ME and retinal hemorrhage); (D) OCT of the same case with resolution of ME and \downarrow CRT at 1 month after first IVA injection.

20/240 (log MAR 1.08) improved to 20/50 (log MAR 0.40) at 1 week after injection and still the same up to 1 month postoperatively ($P < 0.001$). At 3 months the mean BCVA changed to 20/100 (log MAR 0.70) due to recurrence of macular edema in some eyes but still significantly different than baseline ($P < 0.01$). At 6 months the mean BCVA significantly improved again to 20/80 (log MAR 0.60) ($P < 0.001$). At the end of follow-up (about 12 months) further significant improvement to 20/60 (log MAR 0.48) ($P < 0.001$), about halving the baseline visual angle.

At the baseline there were 18 eyes (60%) of all patients had BCVA of less than 20/240, 9 eyes (30%) had BCVA of (range, 20/240–20/50) and 3 eyes (10%) had BCVA of more than (20/50). At the end of follow-up 6 eyes (20%) of all patients had BCVA of less than 20/240, 18 eyes (60%) had BCVA of (range, 20/240–20/50) and 6 eyes (20%) had BCVA of more than (20/50) (Table 3, Fig. 8).

Table 2 demonstrating the number of intravitreal Avastin (IVA) injections all over the study period. The total number of injections was 81 with a mean of 2.7 (range, 1–6 injections) 6–8 weeks interval, 41 injections (mean 3.4) in CRVO eyes, 40 injections (mean 2.2) in BRVO eyes. Twelve eyes (40%) had 3 injections, 12 eyes (40%) had 2 injections, 2 eyes (6.7%) had 1 injection those had BRVO. Four eyes (13.3%) had more than 3 injections those had CRVO, out of them 2 eyes had 4 injections, 1 eye 5 injections and 1 eye 6 injections.

There were great proportional decrease in venous tortuosity, optic disc edema and surface wrinkling after 1 month of injection. No evidence of increase foveal a vascular zone demonstrated by (FA), no neo-vascularization. Neither systemic nor intraocular adverse events were reported except mild degree of sub-conjunctival hemorrhage in 5 eyes that resolved spontaneously within 5 days of injection.

4. Discussion

Retinal vein occlusions are the second most common form of retinal vascular disease with a prevalence of 0.5–1.0% (Klein et al., 2000). Depending on the location of the occlusion and the extent of non-perfusion, the vision threatening complications of retinal vein occlusions include neo-vascularization of the retina or optic nerve causing recurrent vitreous hemor-

Table 1 Mean CRT and mean BCVA at baseline and follow-up.

Timing	Mean (SD) {range} CMT (μm)	Dif. CMT (μm)	P value	Mean BCVA	log MAR (SD)	P value
Baseline	455 (± 126) {386–510}			20/240	1.08 (± 0.52)	
1 week	280 (± 72) {240–340}	175	< 0.01	20/50	0.40 (± 0.25)	< 0.0001
1 month	356 (± 118) {296–416}	99	< 0.02	20/50	0.40 (± 0.27)	< 0.0001
3 months	302 (± 86) {270–368}	153	< 0.01	20/100	0.70 (± 0.30)	< 0.001
6 months	402 (± 170) {338–468}	53	< 0.06	20/80	0.60 (± 0.42)	< 0.001
12 months	250 (± 48) {200–298}	205	< 0.001	20/60	0.48 (± 0.32)	< 0.0001

P value considered to be statistically significant if it is < 0.05.

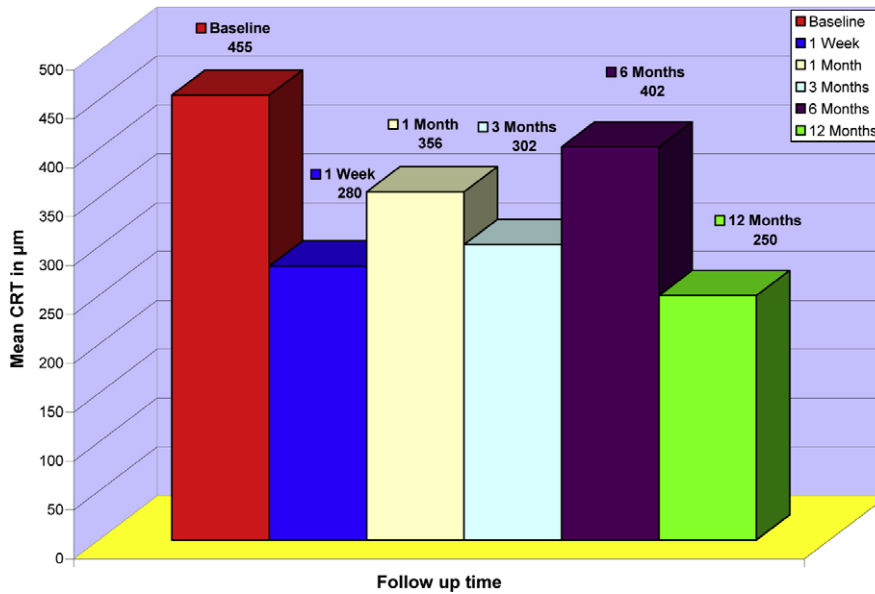


Figure 6 The mean CRT in μm measured with OCT.

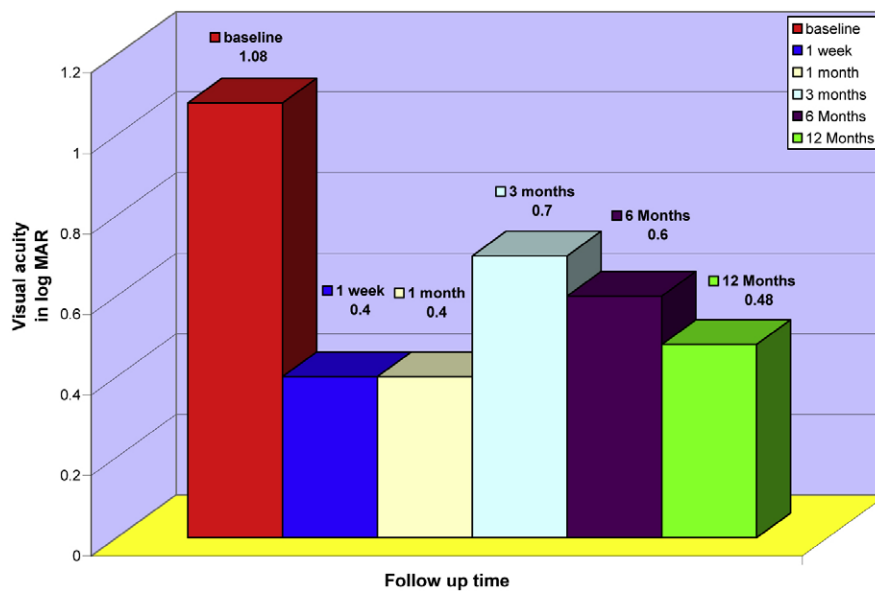


Figure 7 Visual acuity in log MAR in over time.

rhage, neo-vascular glaucoma, macular ischemia, macular edema, surface wrinkling retinopathy, capillary non-perfusion, and intraretinal hemorrhage. The endogenous production of

vascular endothelial growth factor (VEGF) has been implicated as an etiologic factor for several of these complications (Pe'er et al., 1995).

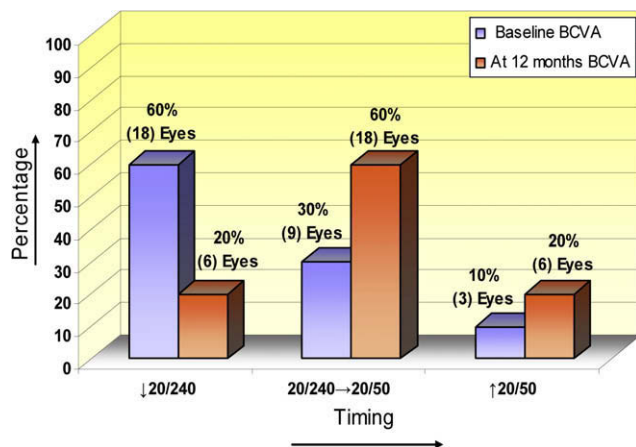


Figure 8 BCVA improvement with follow-up time.

Table 2 Number of injections for each eye in the studied patients.

Number of injections	12 eyes of CRVO	18 eyes of BRVO	Total number of eyes (%)
1 injection	0	2	2 (6.7%)
2 injections	2	10	12 (40%)
3 injections	6	6	12 (40%)
4 injections	2	0	2 (6.7%)
5 injections	1	0	1 (3.3%)
6 injections	1	0	1 (3.3%)
Total number of injection (mean)	41 (3.4)	40 (2.2)	81 (2.7)

Table 3 BCVA improvement with follow-up time.

Timing	BCVA	Number of eyes	Percentage (%)
Baseline	(1) ↓ 20/240	18	60
	(2) 20/240→20/50	9	30
	(3) ↑ 20/50	3	10
At 12 months	(1) ↓ 20/240	6	20
	(2) 20/240→20/50	18	60
	(3) ↑ 20/50	6	20

Vascular endothelial growth factor (VEGF) has been implicated as the major factor responsible for increased vascular permeability and ME in CRVO. Vascular endothelial growth factor was shown to be up-regulated in human eyes with CRVO (Tolentino et al., 2002; Pe'er et al., 1998; Vinoso et al., 1997). In addition, VEGF injections into the vitreous of a nonhuman primate eye resulted in a CRVO-like appearance characterized by retinal ischemia, intraretinal hemorrhages, and retinal edema (Tolentino et al., 2002). If VEGF is responsible for the ME in CRVO, then one strategy would be to treat the ME by inhibiting VEGF with an anti-VEGF drug such as bevacizumab (Avastin, Genentech, Inc., San Francisco, CA), a full-length, humanized, monoclonal antibody directed against VEGF.

In May 2005 at the Bascom Palmer Eye Institute, bevacizumab was first injected into the vitreous of an eye with

ME from CRVO (Rosenfeld et al., 2005). Within 1 week of the bevacizumab injection, the patient's VA improved from 20/200 to 20/50 and optical coherence tomography (OCT) imaging showed resolution of the cystic maculopathy characteristic of ME. Since this initial report, intravitreal bevacizumab has been used with increasing regularity as the primary pharmacotherapy for CRVO at the Bascom Palmer Eye Institute. Intravitreal bevacizumab for vein occlusions is now being used worldwide and multiple small case series with short follow-up have already been reported (Costa et al., 2007; Ferrara et al., 2007).

A number of recent studies have shown promising short-term effects of bevacizumab when used for ME associated with BRVO or central retinal vein occlusion (Kriechbaum et al., 2008; Moschos and Moschos, 2008; Hsu et al., 2007; Matsumoto et al., 2007; Iturralde et al., 2006). After intravitreal injection of bevacizumab, optical coherence tomography (OCT) demonstrates an immediate reduction in foveal thickness and an improved visual acuity. In most reports, the morphologic effect of bevacizumab was studied based on foveal thickness measured by OCT and visual function evaluated by visual acuity measurement.

In our study intravitreal Avastin (IVA) injection was used as a primary treatment for RVOs and it was noticed that visual acuity and CRT improved after a relatively short time within 1 week after first IVA injection in which visual acuity improved from mean of 20/240 or 1.08 (± 0.52) log MAR at baseline to 20/50 or 0.40 (± 0.25) log MAR which it was statistically significant $P < 0.0001$. CMT improved also, from mean of 455 μm (± 126) SD {range, 386–510} at baseline to 280 μm (± 72) SD {range, 240–340} with a difference of 175 μm within 1 week. This improvement in both of visual acuity and CRT lasted for about 6 weeks then, started to deteriorate again with need for re-injection. However there is a variation from 1 patient to another in which 2 eyes with BRVO cured by one IVA injection only while others with CRVO showed recurrence with need for 5–6 re-injections. The response for improvement and recurrence depend of degree of macular ischemia, amount of retinal hemorrhages, extend of irreversible photoreceptor damage and progression over time from perfused to nonperfused RVOs.

In the current study, all eyes either with CRVO or BRVO showed improvement and some showed recurrence and re-injection with stability of visual acuity and absence of ME, mean CRT was 250 μm (± 48) {range, 200–298} with maximum difference than the mean baseline in which it was 205 μm difference at the end of follow-up with mean visual acuity of 20/60 or 0.48 (± 0.32) log MAR indicating great usefulness of IVA in management of RVOs.

Our results in agreement with the results of Noritatsu et al. (2009), in which they studied prospectively IVA injection in 20 eyes of 20 patients with RVOs (6 patients with CRVO and 14 with BRVO) in which the CRT decreased from mean of 560 μm (± 123) at baseline to 391 μm (± 145) after 6 months of repeated injections. Also, our results in agreement with Sherif (2008), in which he studied IVA injection in 15 eyes of 15 patients with RVOs (10 eyes with CRVO and 5 with BRVO) in which the CRT decreased from mean of 625 μm at baseline to 200 μm after 12 months of repeated injections and improvement of visual acuity from 20/100 at baseline to 20/40 at the end of 12 months follow-up. Our mean number of IVA injection was 2.7 in agreement with Sherif's results

of 2.4 in the same period of 12 months post-injection follow-up in spite of he used higher dose of 0.1 ml (2.50 mg) that is double our dose.

No intraocular or systemic adverse effects were reported in our study during the 12 months of follow-up such as increased intraocular pressure (IOP), retinal tear, retinal detachment, induced cataract formation, inflammation, infection, systemic hypertension or thromboembolic events and hence IVA seems to be safe and effective in treatment of RVOs. Limitations of the current study are relatively short-term follow-up, small sample size, and lack of a control group.

In conclusion, despite these promising results there are some risks of intravitreal injection of bevacizumab, further long term randomized prospective controlled large studies are necessary to confirm the efficacy of bevacizumab and to determine the ideal protocol for this promising recent treatment.

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