Role of Intravitreal Injection bevacizumab (Avastin®) in Macular Edema after Central Retinal Vein Occlusion

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Introduction: No effective treatment modality has been found for vision loss in central retinal vein occlusion (CRVO). But in some studies with short follow up, cystoid macular edema (CME) has responded to bevacizumab with subsequent improvement in vision.

Purpose: To study effects of bevacizumab in the resolution of CRVO.

Materials and Methods: This case series included 32 patients presenting with CRVO having CME. An injection of 1.25 mg bevacizumab (Avastin) in 0.05 ml was given to all patients. Individual response to treatment was checked by best corrected visual acuity (BCVA), optical coherence tomography (OCT), fluorescein angiography, and tonometry and based on that re-injection was considered.

Results: Follow-up was 4 months; mean number of injections was 2.2 (range, 2−3) per patient. Baseline central macular thickness was 665.25 (mean) +/- 187.63 µ. Statistically significant reduction of macular thickness ($P < 0.001$) was seen at six weeks (mean 280.37 +/- 93.31µ); 12 weeks (mean 305.12 +/- 54.26µ) and 16 weeks (mean 270.37 +/- 50.89µ). Significant BCVA improvement was seen at six weeks (mean, 6/60 Snellen), and 16 weeks (mean, 6/60 +/-2 Snellen) from baseline best corrected visual acuity (mean, 4/60). Also, 23 patients (71.85%) had BCVA improvement at the last follow-up.

Conclusion: In CRVO patients, CME has shown positive response to intravitreal injection of bevacizumab. Reinjections if given at appropriate time can result in better visual outcome.

Keywords: Bevacizumab, central retinal vein occlusion, macular oedema

Introduction:

In spite of high incidence of CRVO, its pathogenesis is still not fully understood. Most of the rubeotic eyes after CRVO were shown to have venous thrombi by Green et al, but it is not known whether venous thrombosis occurs as the precursor or the consequence in the chain of events[1].

The main cause of decreased visual acuity (VA) in CRVO is the cystoid macular edema. The permeability of microvasculature of the retina is increased secondary to decreased function of endothelial blood retinal barrier which in turn is due to the impaired microcirculation. This results in exudation into the central retina. Theoretically normalization of retinal perfusion should improve the situation; however strangely, randomized studies have shown limited benefit from hemodilution therapy[2-4]

Once the macular edema has developed, it is necessary to treat it because it can damage the photoreceptors permanently in three months of its development[5,6]. Studies have shown Grid laser photocoagulation the effectiveness of in reducing the macular edema in patients with branch retinal vein occlusion (BRVO), however its effectiveness in cases of CRVO is negligible[7,8]. Another effective treatment modality is the intravitreal injection of triamcinolone (IVTA). However, recent studies have shown their reduced effectivity after one year despite repeated injections, also its complications like glaucoma, cataract formation or endophthalmitis are quite undesirable[9-12]. The main cause of macular edema, is thought to be VEGF similar to CRVO [13], and intravitreally injected antiVEGF antibodies are the latest treatment modality in the management of retinal venous occlusion[14].

Bevacizumab (Avastin®, Genentech®) and pegaptanib (Macugen®), were one of first antiVEGF antibodies developed for the treatment of CRVO-induced macular edema[15-17.] Studies have shown that they result in significant reduction in central retinal thickness (CRT) with improvement of visual acuity[14,18]. Only short- to moderate-term reports or retrospective studies are available in the literature for the management of macular edema secondary to CRVO with bevacizumab[14,18]. The current study evaluates changes in Visual Acuity, and morphological changes in the retina to treatment with bevazicumab, along with safety of the drug.

Objective:

To evaluate the usefulness of injection avastin (bevacizumab), given intravitreally, in patients developing Macular Edema after Central Retinal Vein Occlusion.

Materials And Methods:

Patients presenting with CRVO having CME in the outpatient department of the Institute of Ophthalmology, Mayo Hospital, Lahore from 1st February 2010 till 31st October were included in this study. There were total 32 patients comprising 18 male and 14 female patients. it was a nonrandomized interventional case series. Informed consent was taken from all patients regarding three special aspects of bevacizumab

1. Off label character
2. Systemic side effects
3. Unknown long-term complications of the drug.

Inclusion criteria

1. CRVO, diagnosed on fundoscopy and confirmed by fundus angiography, with macular edema of more than 250 µm measured by optically coherent tomogram (OCT) and for the duration of not more than four weeks.
2. Age older than 18 years.
3. Non ischaemic CRVO

Exclusion criteria

1. Patients with conditions requiring immediate photocoagulation (e.g., retinal, angle or disc neovascularization).
2. Systemic conditions resulting in macular edema.
3. History of hypersensitivity or allergy to bevacizumab.
4. Pregnant ladies.

Patients with a recent history of stroke/ischemic heart disease.

All patients were given intravitreal injection of 1.25 mg bevacizumab in 0,05ml over pars plana area under aseptic conditions after undergoing baseline investigations including best corrected visual acuity, tonometry fundus fluorescein angiography, detailed fundus examination, and optical coherence tomography,. After six weeks of follow-up time, response to treatment was checked with the help

of OCT and based on that reinjection of bevacizumab was considered. The primary outcome, measured by OCT, shows the reduction in macular edema. Baseline visual acuity was measured by Snellen and later on at each follow-up visit (1st week and then 6 weeks, 12 weeks and 16 weeks after injection). The following data information was recorded: patient demographics, complete ophthalmic history and complete ocular examination including BCVA (Snellen), OCT, applanation tonometry, gonioscopy and relevant medical history, duration of vein occlusion prior to injection,. fluorescein angiographic documentation of retinal changes was done preoperatively and between 6, 12 and 16 weeks post-injection.

FFA was done to study capillary non-perfusion areas to differentiate ischemic from non-ischemic CRVO and to assess status of macular hypoperfusion. All other parameters were evaluated on day 0 6, 12 and 16 weeks post injection along with assessment of any side effects.

Significant difference between the paired groups was analyzed statistically by the Wilcoxon signed rank test. Statistically significant difference between two independent groups was calculated by Mann-Whitney test whereas overall significance was calculated by using Friedman Multiple Comparison test. All these statistical analysis were performed using the SPSS in Windows.

Results:

#	Age, Sex	Study Eye	Total Ischemic Area (DAs)	Pre Injection		1st week Post Injection		6th Week Post Injection			12th Week Post Injection			16th Week Post Injection	
			DA= 1.77mm	OCT CMT	BCVA (Snellen)	OCT CMT	BCVA (Snellen)	OCT CMT	BCVA (Snellen)	Inj. Given	OCT CMT	BCVA (Snellen)	Inj. Given	OCT CMT	BCVA (Snellen)
1	56y, M	OD	56	728	3/60	620	3/60	263	3/60	Yes	268	3/60	Yes	236	3/60
2	67y, M	OS	36	455	6/60	348	6/60	188	6/24	No	256	6/36	Yes	233	6/24
3	46y, F	OD	56	875	2/60	672	3/60	462	3/60	Yes	386	2/60	Yes	289	3/60
4	51y, M	OD	>60	984	1/60	792	1/60	432	3/60	Yes	274	1/60	Yes	246	3/60
5	67y, M	OS	32	543	6/60	483	6/60	242	6/24	No	299	6/36	Yes	253	6/24
6	53y, M	OD	45	673	5/60	487	5/60	198	6/36	No	312	6/36	Yes	241	6/36
7	57y, F	OS	39	483	5/60	415	5/60	211	6/60	No	268	5/60	Yes	212	5/60
8	75y, M	OD	>60	988	1/60	813	1/60	442	6/60	Yes	347	4/60	Yes	324	5/60
9	64y, F	OD	55	863	1/60	800	1/60	386	3/60	Yes	305	2/60	Yes	296	3/60
10	57y, M	OD	53	874	2/60	642	2/60	288	5/60	No	322	3/60	Yes	293	6/60
11	71y, M	OS	44	528	4/60	326	4/60	246	6/60	No	294	4/60	Yes	255	6/60
12	72y, F	OD	29	465	6/36	428	6/36	217	6/18	No	304	6/18	Yes	248	6/24
13	59y, F	OD	43	762	5/60	648	5/60	268	6/36	No	308	6/60	Yes	257	6/36
14	65y, M	OD	36	583	5/60	524	5/60	203	5/60	No	285	6/60	Yes	233	5/60
15	64y, F	OS	>60	859	1/60	759	1/60	456	4/60	Yes	385	2/60	Yes	373	3/60
16	69y, M	OD	35	438	6/60	384	6/60	193	6/24	No	276	6/36	Yes	245	6/36
17	65y, M	OD	38	574	6/60	533	6/60	247	6/36	No	297	6/60	Yes	263	6/60
18	58y, M	OD	51	764	2/60	674	2/60	276	2/60	No	311	2/60	Yes	287	4/60
19	53y, F	OD	32	448	5/60	384	5/60	214	6/36	No	278	6/60	Yes	254	6/60
20	67y, F	OS	55	683	1/60	566	2/60	265	5/60	No	284	3/60	Yes	273	4/60
21	74y, M	OS	48	538	3/60	438	3/60	202	4/60	No	220	3/60	No	247	5/60
22	56y, M	OS	52	794	2/60	717	2/60	348	2/60	Yes	318	2/60	Yes	306	2/60
23	65y, F	OD	36	530	6/60	428	6/60	232	6/36	No	235	6/60	No	259	6/36
24	58y, F	OS	31	469	6/60	428	6/60	188	6/24	No	277	6/36	Yes	238	6/36
25	53y, M	OD	27	463	6/36	387	6/36	227	6/36	No	298	6/60	Yes	243	6/36
26	56y, M	OD	39	566	4/60	496	4/60	210	6/60	No	279	4/60	Yes	223	5/60
27	68y, F	OS	37	529	4/60	487	4/60	322	6/60	Yes	256	4/60	No	276	6/60
28	70y, F	OD	>60	1044	2/60	952	2/60	534	2/60	Yes	523	1/60	Yes	486	2/60
29	62y, M	OD	53	893	4/60	721	4/60	267	4/60	No	345	3/60	Yes	297	6/60
30	59y, F	OD	58	854	3/60	627	3/60	262	3/60	No	319	2/60	Yes	265	3/60
31	62y, F	OS	31	511	6/60	449	6/60	234	6/36	No	346	6/60	Yes	246	6/36
32	67y, M	OD	48	527	5/60	482	5/60	249	5/60	No	289	4/60	Yes	255	5/60

The patients were followed for 4 months. The mean number of injections given per patient was 2.2 (range, 2−3 injections per patient). The mean BCVA at baseline was 4/60 Snellen. Using Friedman test, statistically significant BCVA improvement ($p < 0.05$) was seen in 23 patients (71.875%) at six weeks; at twelve weeks; and at sixteen weeks with mean vision 6/60 (Snellen) from the best corrected visual acuity at presentation; mean 4/60. The mean central macular thickness documented on OCT at baseline was 665.25 (±187.63) Microns. Reduction in macular thickness ($P < 0.05$) was seen as following: at six weeks, 280.37 (±93.31) (mean improvement 384.88 μ); and at twelve weeks 305.12 (±54.26) (mean improvement 360.13 μ); and at sixteen weeks 270.37 (±50.89) (mean improvement 394.88 μ), and this was found to be statistically significant. Overall, there was a statistically significant decrease in Central Macular Thickness (CMT) over the study period ($P < 0.05$), Friedman test. 37.5% patients had a CMT 250 microns or less at final follow-up visit while 40.62% patients had CMT in the range of 250-300 microns. Despite this improvement no direct correlation was observed between reduction in macular thickness and improvement of BCVA. On the other hand, the reduction in macular thickness was more marked and preceded BCVA improvement (probably due to the multiple factors determining the latter.) However, there was a general improvement of BCVA associated with reduction in CMT observed throughout the study period.

Discussion:

In central retinal vein occlusion, decrease in visual acuity is due to macular ischemia, edema and photoreceptor death. Therefore, the aims of treatment are

1. Therapy to improve retinal circulation of blood.
2. To prevent occurrence of complications due to CME and neovascularization.

For improving blood circulation, no convincing results of any treatment were shown by studies other than hemodilution.

Avastin (bevacizumab) has been shown to be effective as early intervention for CME. Despite the intravitreal injection of bevacizumab, showing its effectiveness in treating retinal microvascular diseases at present, only few studies have documented the role of intravitreal injection of bevacizumab in modifying the course of CRVO. An improvement of VA of 87.5% was found in 16 treated eyes, in a retrospective study, after 3 months[14]. In another retrospective study visual acuity was improved by more than three lines in 40% of the patients[18]. In a 6 month follow up prospective study, Schaal et al demonstrated that 2.5 mg bevacizumab was required to improve VA in 73.3% eyes with CRVO[19].

In our current study, VA and CRT of 32 patients having CRVO were evaluated after 12 week course of bevacizumab injection. Improvement in visual acuity ranged from one to five lines and was achieved between 1st and six weeks after injection. An improvement of two or more lines was shown by 60% of the patients which is in accordance with the currently available data[14,18-20]. Whereas maximum reduction of macular thickness was achieved by 1−2 weeks following the injection, CME was resolved in 71.875% at the end of the study period. This showed that reduction in macular thickness preceded the improvement in visual acuity.

Bevacizumab, overall showed good visual results in patients with both low and high baseline VA. There was general improvement of one to two Snellen lines in patients who presented with good visual acuity, while patients having moderate visual loss (i.e. up to 6/60) showed improvement of visual acuity of two lines or better.

In a prospective study done by Stahl et al, better visual improvement was seen in patients in whom treatment was instituted within three months of onset of CRVO[20]. However, Priglinger et al in a recent study showed no statistically significant difference in early and late injection groups[21]. This might have been due to small sample size or many other factors that can affect visual outcome in patients of CRVO.

Also less improvement was seen in patients with ischemic CRVO compared to patients with non-ischemic CRVO. Due to macular ischemia only 25% of the eyes of ischemic CRVO had 3 lines improvement. In spite of treatment 75% of the ischemic CRVO patients developed neovascularization, and conversion from non-ischemic to ischemic CRVO was seen in two patients. This led to a deduction that the current dose of 1.25mg bevacizumab fails to prevent neovascular complication of CRVO. In a study by Costa et al vascular or ischemic status of retina showed no improvement in spite of using 2mg bevacizumab for ischemic CRVO. It was suggested that further studies are required for any conclusive results[22]. A note must also be made that in studies with smaller number of patients, the subgroup analysis merely indicates tendencies rather than reflecting statistically significant results.

There is a correlation between CRT reduction related to bevacizumab injection and improvement of visual acuity

Regular OCT examinations can help in early detection of decrease in VA even after bevacizumab injection. If there is increased CRT on OCT reinjection may be reconsidered. It is seen from observing the natural course of CRVO that a considerable time may elapse before the establishment of a balanced retinal circulation inflow and outflow. The theory regarding balance in the new blood flow is supported by the fact that there is formation of collateral disc vessels with a new drainage route[23]. It is proposed that treatment with bevacuzimab should be sustained until a new balance is

achieved between retinal inflow/ outflow. This in fact remains the main challenge in this therapy i.e. to give reinjections at appropriate time and interval so that initial improvement in VA can be maintained, along with treatment of secondary complications with laser.

Bevacizumab injection is known to have a positive effect on CRT reduction as well as visual acuity improvement[17,19,23]. Although there was a good response to treatment overall, there was some variability among the individuals, where there was little or no improvement in visual acuity in spite of a decrease in CRT. The cause of this may be macular hypoperfusion, seen as an increased or irregular foveal avascular zone (FAZ), foveal hemorrhage followed by pigment epithelial degeneration. In a few patients, no improvement was seen in CMT or VA beyond third week with bevacizumab injections. We can only assume that the degrees of ischemia, along with other confounding factors may have an impact on response to treatment, because the non-responders were no different from rest of the study population.

The cause(s) behind treatment failure, as well as whether bevacizumab has a negative long-term effect on collateral formation because of its antiVEGF action needs to be evaluated by further studies.

Conclusion:

In summary, most of the patients with CRVO showed significant improvement in VA and resolution of macular edema after bevacizumab therapy. This response apparently might have been due to decrease in vascular permeability like that seen with intravitreally administered corticosteroids, though without the undue rise in intraocular pressure. In our study, other complications documented in the literature like cataract, intraocular inflammation, endophthalmitis, central retinal artery occlusion or retinal detachment[24,25] were not observed. Thus it is suggested that treatment with intravitreal bevacizumab should be given under close postoperative observation, and only after taking into consideration the OCT and VA findings, repeat dose may be administered at six weeks, until stability is achieved.

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