Clinical Utilisation of Bevacizumab and Patient Monitoring in Retinal Vein Occlusion and Diabetic Macular Edema

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ABSTRACT

Purpose: To estimate the utilization of bevacizumab and to monitor disease in patients with the branch or central retinal vein occlusion (BRVO/CRVO) and diabetic macular edema (DME) in clinical practice.

Material and methods: This hospital-based prospective study comprised 102 patients with macular edema with DME and RVO. Intravitreal injection of 1.25 mg/0.05ml Bevacizumab was administered following standard surgical protocol. All eyes were bi-microscopically examined preoperatively and post-operatively.

Results: As per the optical coherence tomography (OCT) results of Central Foveal Thickness (CFT), the amount of CFT in DME patients reduced to 278.20 ± 68.91(initial: 511.02 ± 131.92); in BRVO patients, it was reduced to 219.04 ± 53.61 (initial: 425.83± 151.68); and in CRVO patients, it was reduced to 292.14 ± 46.99 (initial: 598.71 ± 87.27) after the injection at the end of 1 year. There was significant difference observed between the initial and end of follow-up CFT ($p<0.0001$).

Conclusion: The study showed that the intravitreal Bevacizumab is an effective and way to treat macular edema related to diabetic eye disease and retinal vein occlusion.

Keywords: Branch retinal vein occlusion, Central retinal vein occlusion, Diabetic macular edema, Bevacizumab, Optical coherence tomography.

INTRODUCTION

Retinal vein occlusion (RVO) is considered to be one of the most common causes of acquired retinal vascular abnormality resulting in frequent loss of vision. There are few data available on the predominance of RVO in the general population even though it was documented way back in early 1855. Several data have been recently acknowledged from studies including mostly white population and others including Chinese, Hispanics, and Asian Malays.[1] RVO [categorized into central (CRVO) and branch (BRVO)] and diabetic macular edema (DME) are among the most common retinal vascular diseases accountable for the loss of vision. RVO and DME are expected to affect approximately 16.4 and 21 million people worldwide individually.[2] CRVO is estimated to affect approximately 2.5 million people globally causing loss of vision. The upregulation of hypoxia-regulated genes i.e. vascular endothelial growth factor-A (VEGF-A), a primary mediator in CRVO-associated macular edema is thought to be the vital pathogenic mechanism of retinal ischemia resulting to venous occlusion leading to visual impairment in patients.[3,4]

Diabetic retinopathy manifests itself as Diabetic macular edema (DME) that produces loss of central vision. DME is triggered by excessive vascular permeability, ensuing the leakage of fluid and plasma constituents (mainly lipoproteins) into the retina resulting in the thickening of the retina.[5] Vascular endothelial growth factor (VEGF) is an endothelial growth and permeability factor that aids in physiological vasculogenesis and angiogenesis in the embryo. It plays a role in the formation of pathologic blood vessels, in tumor growth and ocular diseases. The main factor for an increased VEGF is hypoxia and transforming growth factor (TGF). The augmentation VEGF levels cause increased vascularity and depositing collagen thus, producing a scar; while counteraction of VEGF reduces angiogenesis and cutaneous fibrosis.[6] Intravitreal anti-

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VEGF drugs have been a beneficial therapy for patients with macular edema secondary to CRVO. The efficacy of anti-VEGF drugs in CRVO has been documented in several studies. Intravitreal bevacizumab (IVB), a novel treatment possibility has been presented for early intervention against the formation of cystoid macular edema (CME).[7] This study aimed to examine the utilization of bevacizumab and to monitor disease in patients with the branch or central retinal vein occlusion (BRVO/CRVO) and diabetic macular edema (DME) in clinical practice.

MATERIALS AND METHOD

It is a hospital-based prospective non-controlled interventional study, consisted of 102 subjects. Patients attended at Sankar Foundation Eye institute with Macular edema along with Retinal Veins Occlusions and Diabetic Retinopathies were included in the study during May, 2018- April, 2019. The study protocol has been approved by the Institutional Ethics committee, Sankar Foundation Eye institute, Visakhapatnam, Andhrapradesh, India. Informed consent was obtained from the patients prior to the treatment. Before initiation of the treatment, all patients undergo a standard slit lamp ophthalmologic examination of the anterior and posterior segments with a 90D/78D lens as well as with indirect Ophthalmoscope. Best Corrected visual acuity (BCVA), intraocular pressure, and Central Foveal Thickness in Oct are measured. The standard protocol for intravitreal injections includes topical anesthesia, disinfection, and lid speculum. Eyes are anesthetized with topical proparacaine hydrochloride drops. Intravitreal injection of 1.25 mg/0.05ml bevacizumab is performed in the Operation theatre at the inferior-temporal part of the eyeball 3.5 mm away from the limbus for pseudophakes, 3 mm away from limbus for aphakic eyes and 4 mm away from the limbus for phakic eyes with needle direction towards the center of the globe. All eyes are biomicroscopically examined preoperatively, on postoperative day 1, 7 and at 1, 2, and 3 months. At monthly visits, visual acuity, and central foveal thickness by Oct is measured.

Inclusion criteria: Freshly diagnosed disease with no history of any previous medical or any other mode of treatment for the same.

Exclusion criteria: 1. Patients with diagnoses of more than one of the retinal diseases that are commonly treated with anti-VEGF agents (i.e., BRVO, CRVO, DME, and nAMD)**.** 2. Any intra-ocular surgeries, intravitreal steroids, or laser photocoagulations (i.e. PRP, Macular grid/focal photocoagulations) within 3 months of initiation of bevacizumab therapy. 3. Presence of significant media opacities (e.g. significant cataracts, vitreous hemorrhages, corneal scar)

Statistical Analysis:

The results were presented in mean ± standard deviation and percentages. Statistical analysis calculates the difference between the observed means in two CMT and BCVA independent samples. A significance value (P value) and 95% Confidence Interval (CI) of the difference is reported. Student's t-test performed to identify the significantly difference between the baseline and post surgery variables. A p-value less than 0.05 (typically ≤ 0.05) is statistically significant. Statistical analysis was done using SPSS Version 17 (SPSS version 22, SPSS Inc, Chicago, IL).

RESULTS

Of the total number of patients diagnosed with BRVO, CRVO, and DME, a total of 102 patients met all inclusion and exclusion criteria. All these patients received treatment with Bevacizumab. The total number of cases included 34 (53.1%) male and 30(46.9%) female DME, 13(54.2%) male; 11(45.8%) female with BRVO and 8(57.1%) male; 6(42.9%) female with CRVO patients. Among these patients, 54.2% with BRVO, 64.3% with CRVO, and 31.25% with DME were 60 years of age or older. Approximately 50% of each diagnostic group were male. (DME: 52.12%, BRVO: 54.17%, 64.28%).

Anti-VEGF utilisation*:*

The time taken for the 1st dose of Bevacizumab injection after the diagnosis are generally same, despite small fluctuations related to the severity of the disease (i.e. the more severe the disease the less the time between the diagnosis and the 1st injection). Although this needs to be examined on a larger sample size using some different study method to draw a concrete conclusion. Further analysis indicated that most annual injections were received in the first 6 months of treatment.

Anti-VEGF utilisation in DME: A total of 64 patients (64 eyes), Male: 34 (53.12%) Age 60 or above: 20 (31.25%), are subjected to in this study regarding Diabetic Macular Edema. As per the OCT results of Central Foveal Thickness (CFT), the amount of CFT in DME patients reduced to 278.20+-68.91 after the injections at the end of 1 year. The initial amount of CFT was 511.02±131.92.The mean number of Bevacizumab injection given was 5.2 at the end of 1 year.

Anti-VEGF utilisation in BRVO: A total number of 24 patients (24 eyes) were subjected to this study regarding BRVO. Male: 13 (54.17%) Age 60 or above: 13 (54.17 %). As per the OCT results of Central Foveal Thickness (CFT), the amount of CFT in BRVO patients reduced to 219.04+-53.61 after the injection at the end of 1 year. The initial amount of CFT was 425.83± 151.68.Mean BCVA (beginning) (in logMAR units): 0.754 ± 0.386 Mean BCVA

(end) (in logMAR units): 0.246 ± 0.209. The mean number of Bevacizumab injection is 3.2 at the end of 1 year.

Anti-VEGF utilisation in CRVO: A total of 14 patients (14 eyes) were subjected to this study regarding CRVO. Male: 8 (57.14 %) Age 60 or above: 9 (64.28 %). As per the OCT results of Central Foveal Thickness (CFT), the amount of CFT in CRVO patients reduced to 292.14±46.99 after the injection at the end of 1 year. The initial amount of CFT was 598.71±87.27. The mean number of Bevacizumab injection is 2.2 at the end of 1 year.

DISCUSSION

Retinal vein occlusion (RVO) being the most common retinal vascular disease second to diabetic retinopathy; is largely categorized as either CRVO, hemispheric retinal vein occlusion (HRVO), or BRVO. The existence of macular edema in retinal vein occlusion has been documented to cause vision loss most commonly.[8]

BRVO is the most common type of RVO with an informed prevalence rate of 4.42 cases per 1000. (1) Vascular endothelial growth factors (VEGF) were believed to have an imperative role in the pathogenesis of ME in BRVO. Anti-VEGF agents such as bevacizumab (IVB), aflibercept (IVA), and ranibizumab (IVR) have been established to be harmless and efficient in treating BRVO. IVB has been used as an off-label drug in patients with ME in BRVO proving to be successful within a period of 6 to 24 months.[9]

Macular edema (ME) due to RVO is the second most common retinal vascular condition often resulting in vision loss. Intravitreal pharmacotherapy with corticosteroids and drugs that bind VEGF mostly treats the edema and improves visual acuity. This has proven to be superior to cases with CRVO and also better than laser photocoagulation in eyes with branch BRVO.[10] Diabetic macular edema (DME) is a manifestation of diabetic retinopathy producing loss of central vision. ME within 1 disk diameter of the fovea is present in 9% of the diabetic population. In patients with type 1 diabetes visual loss is due to proliferative changes while in type 2 diabetes it is mostly due to macular edema.[5]

It is believed that retinal hypoxia plays an imperative role in DME. VEGF is upregulated by hypoxia and precisely attributes to excessive vascular permeability resulting in macular edema in people with diabetes. Several studies have documented a correlation of VEGF levels with the severity of diabetic retinopathy and also a reduction in levels after successful laser treatment of diabetic retinopathy. Thus

Table 1. Mean CMT improvement (in microns)

Disease Group	Mean	Standard Deviation	Improvement/ Difference	SE	95% CI	t value	P value
DME							
Baseline	511.02	131.92	232.820	18.604	196.0028 to 269.6372	12.514	< 0.0001*
Final	278.20	68.91					
BRVO							
Baseline	425.83	151.68	206.79	32.839	140.6895 to 272.8905	6.297	< 0.0001*
Final	219.04	53.61					
CRVO							
Baseline	598.71	87.27	306.57	26.490	252.1189 to 361.0211	11.573	< 0.0001*
Final	292.14	46.99					

*significant change observed in mean CMT. The significance level is calculated using the t-test.

Table 2. *Mean BCVA improvement (Logmar).*

Disease Group	Mean	Standard Deviation	Improvement/ Difference	SE	95% CI	t value	P value
DME							
Baseline	0.572	0.254	0.350	0.036	0.2785 to 0.4215	9.686	< 0.0001*
Final	0.222	0.138					
BRVO							
Baseline	0.754	0.386	0.508	0.090	0.3276 to 0.6884	5.670	< 0.0001*
Final	0.246	0.209					
CRVO							
Baseline	1.182	0.343	0.391	0.130	0.1230 to 0.6590	2.998	< 0.0001*
Final	0.791	0.347					

*significant change observed in mean **BCVA**. The significance level is calculated using the t-test.

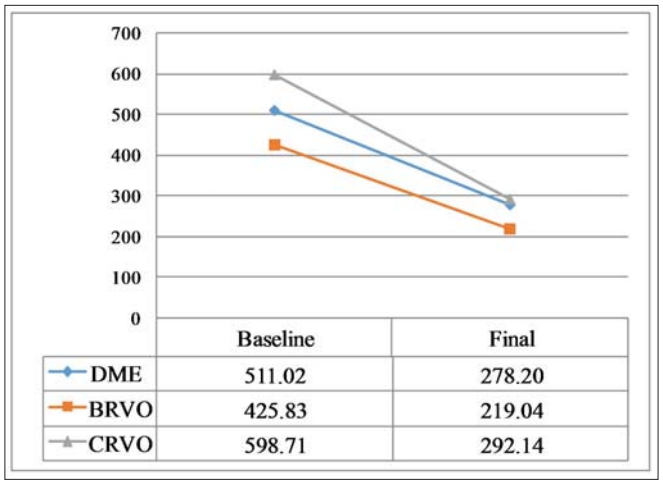

Figure 1. *Mean CMT improvement (in microns).*

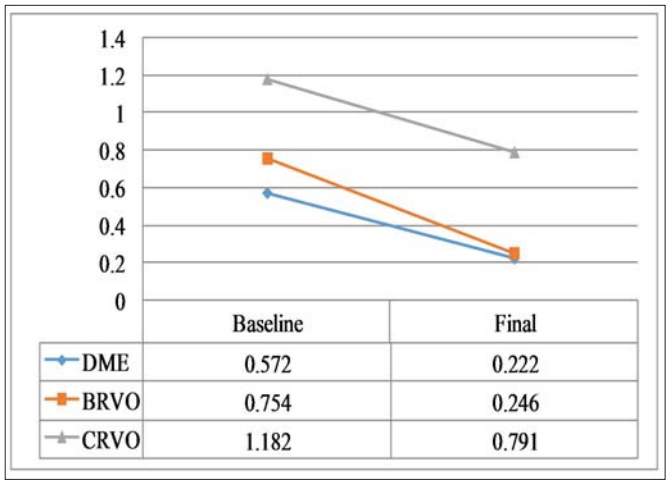

Figure 2. *Mean BCVA improvement (Logmar).*

a coherent approach in treating macular edema in these patients would include the use of anti- VEGF agents.[5]

VEGF contributes to vascularization and fibrosis of tissues and aids in wound healing.[6] This twofold mechanism of VEGF molecules has the potential to influence diseases where there is significant pathologic appearance of VEGF or when it is necessary to modify the normal healing response (e.g. glaucoma filtering surgery). All the anti-VEGF agents that are currently implemented to treat ocular conditions have also been applied precisely in glaucoma management and surgery. Some of the drugs including Pegaptanib (Macugen, Pfizer, New York), bevacizumab (Avastin, Genentech Inc., San Francisco, CA), ranibizumab (Lucentis, Genetech Inc., San Francisco, CA), and aflibercept (Eylea, Regeneron, New York) differ in their affinity for VEGF subtype molecules.[11]

Bevacizumab (IVB) is used as an off-label alternative to anti-VEGF agents (ranibizumab and aflibercept) in the treatment of macular edema (ME) caused due to retinal vein occlusion (RVO), however, not many studies encouraging this approach have been stated. Hence, decisive comparative studies with available anti-VEGF agents regarding efficacy, safety, and cost are needed to be documented.[12]

IVB is a monoclonal antibody against VEGF, that has proven evidence of its efficacy and safety as an intravitreal drug as compared to ranibizumab (IVR) and aflibercept (IVA). In BRVO, vascular occlusion induces the upregulation of VEGF, resulting in increased vascular permeability and subsequent ME. Thus, this provides the basis to use intravitreally injected anti-VEGF to treat BRVO. Many clinical studies are stating the beneficial effects of anti-VEGF therapy for ME following BRVO.[13]

Avery RL et al. (2006) showed short-term results wherein intravitreal IVB was well tolerated and associated with a rapid weakening of retinal and iris neovascularization secondary to proliferative diabetic retinopathy.[14] Manayath GJ et al. (2009) documented the efficiency of intravitreal bevacizumab for treating cystoid macular edema in CRVO patients also advocating the use of reinjections at an appropriate timing, based on the OCT findings for better visual consequence.[7] Prager F et al. (2009) have reported a prospective case series of patients with ME due to RVO and treated with bevacizumab (IVB), showing a mean increase in visual acuity of 16 letters at the 12-months follow up. Subgroup analysis showed a better response in patients with BRVO rather than CRVO, although the reduction in central retinal thickness (CRT) on optical coherence tomography (OCT) was comparable in both subgroups.[15] Rajendran R et al. (2012) provided evidence in their study supporting longer-term use of IVB for persistent ME.[16]

Hikichi et al. in a study on 105 treatment naïve eyes with ME due to BRVO reported significantly improved visual outcome (log MAR 0.64 ± 0.24 to 0.34 ± 0.21) at 2 years follow-up with a mean of 3.8 ± 1.5 IVB injections.[17] Paulose et al. in a study of nine eyes of persistent or recurrent ME because of RVO (both branch and central) reported modest improvement in BCVA using Ziv-aflibercept (IVZ) (Δ ± 0.29 logMAR; P = 0.13) with a significant reduction in CMT (604 ± 199 µm to 351 ± 205 µm; P = 0.02) at 4 months.[10] These conclusions were amenable to the present study that was done with IVB. However, Eldeeb M et al. in their study showed Ziv-aflibercept achieved favorable intermediate-term functional and structural outcomes in ME secondary to CRVO, without any safety concerns.[4] Braimah IZ et al. compared the efficacy of intravitreal bevacizumab (IVB) versus Ziv-aflibercept (IVZ) in BRVO and found that IVZ was more cost-effective with the similar visual result and less number of visits in comparison to IVB.[9] Vader MJC et al. has shown, that bevacizumab is non-inferior to ranibizumab (IVR) for patients with ME resulting from RVO of either subtype when receiving monthly injections for 6 months

based on the change in visual acuity. Based on their findings, the authors stated that IVB might be an efficient substitute for ranibizumab.[12]

Wang JK et al. (2016) had reported intravitreal aflibercept (IVA) and bevacizumab (IVB) had similar efficacy and duration of treatment for macular edema associated with BRVO during 12 month period and there were no serious systemic or ocular adverse events. The authors did not find any significant difference in the visual and anatomic outcomes in their study of 50 eyes with ME associated with BRVO treated with IVA and IVB.[18]

Although IVA and IVB share the same molecular structure, the difference exists in their osmolarity (IVA: 300 mOsm/kg vs IVB: 1000 mOsm/kg) of the difference in purification methods and use of different buffer solutions.[9] The understanding of VEGF as a key mediator of abnormal vascular permeability in the diabetic eye led to early investigations of anti- VEGF therapy for the treatment of DME. The anti-VEGF medication bevacizumab had been developed to bind VEGF in cancer patients and, initially, received approval for the indication of metastatic colon cancer but was not approved for ocular treatment. However, it was subsequently tried as therapy for patients with DME, first systemically, and then intraocularly as off-label use.[19]

In India, a single-use vial of ranibizumab (IVR) costs 17500– 71000INR. A single-use vial of aflibercept (IVA) costs about 56700INR and of bevacizumab (IVB) 100 mg costs about 28000INR. Ten to 18 doses of bevacizumab for ophthalmic use can be prepared from a single vial, costing 1500–2800INR; [approximately 30–50 times less than ranibizumab and 20-38 times less than aflibercept].[13] The overall cost of the treatment with intravitreal anti-VEGF agents include transportation cost to the hospital, hospital fees, investigation charges such as OCT, fluorescein angiography, cost of the anti-VEGF drug, and time spent by the patient and the attendant.[9]

The present prospective study examined the effect of Bevacizumab in ME caused by diabetic retinopathy and RVO. In the present study 3 monthly Bevacizumab injections (loading dose) were administered, followed by PRN (3+PRN) injections. The study showed that intravitreal Bevacizumab is an effective way to treat macular edema related to diabetic eye disease and retinal vein occlusion. Similar to findings in previous clinical trials CFT in SDOCT significantly decreased from baseline during the treatment period and mean BCVA increased. Moreover, the study showed that the DME group of patients requires relatively more injections than retinal vein occlusion patients and the amount of reduction in CFT can be seen more in CRVO patients followed by DME and BRVO patients. But the vision analysis shows that the BRVO group of patients improved the most followed by DME and CRVO group of patients at the end of 12 months. However, the limitation of the study is that it does not have any control group and is not a masked study. The relatively small sample size limits the conclusion regarding the effect of Bevacizumab on the CFT caused by DME and RVOs. So larger, multicentre, prospective, controlled studies are required to better define the efficiency of the drug in patients with macular edema due to RVOs.

CONCLUSION

The study showed that intravitreal Bevacizumab is an effective way to treat macular edema related to diabetic eye disease and retinal vein occlusion. Our study supports IVB treatment as a cost-effective alternative to others in day to day clinical practice.

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