Bevacizumab in management of diabetic macular edema- Bashundhara Eye Hospital Experience

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Abstract

Introduction: *Diabetic retinopathy (DR) is a leading cause of vision loss among working-age population and is related to 1%-5% of cases of blindness worldwide. Anti-VEGF therapy is an effective tool in the management of DME. The purpose of this study was to assess the effectiveness of intravitreal injection of Bevacizumab in the treatment of DME regarding the improvement of best corrected visual acuity (BCVA) and the reduction of central macular thickness (CMT) in Bashundhara Eye Hospital & Research Institute.*

Methods: *The medical records of patients treated with Bevacizumab due to DME at Bashundhara Eye Hospital & Research Institute, between January, 2018 and March, 2022.After applying inclusion and exclusion criteria, 306 patients (368 eyes) were included in the study.*

Results: *Baseline BCVA was worse than 20/40 (mean 20/80; range 20/300–20/50). Baseline central retinal thickness (CRT) was >275ìm (mean 450 ± 28.39µm, range 114–1000). Around half of the study population (162, 52.94 %) was injected Bevacizumab more than thrice, and the rest of the patients were injected three times during the study period. After the application of three consecutive Bevacizumab injections, BCVA was improved 20/80 in 139 (46.8%) patients and after the application of more than three injection, mean BCVA was improved 20/60 in 158(53.2%) patients. The mean CMT level of the study population after three consecutive anti-VEGF therapy (n=139) was 280±17.02µm. Mean CMT level of study population after more than three anti-VEGF therapy (n=158) was 250±7.42 µm. 9 (2.94%) patients having uncontrolled DM showed no improvement in CMT level & BCVA after intra-vitreal injection.*

Conclusions: *Intravitreal Bevacizumab injections significantly improve visual acuity and decrease central macular thickness in patients with diabetic macular edema.*

Key Words: *Diabetic macular edema (DME), Vascular Endothelial Growth Factor (VEGF), Bevacizumab, Central Macular thickness (CMT)*

Introduction

Diabetic retinopathy is frequently caused by diabetic macular edema (DME). The global prevalence of diabetic retinopathy (DR) is 27.0%; varying from 3.8% in the US to 17.2% in Sudan[1–3]. DME arises when breakdown of the blood-retinal barrier leads to increased vascular permeability[4]. VEGF causes the extracellular accumulation of fluid from the intravascular compartment by disturbing the intercellular tight junctions normally present in retinal endothelial cells. The avenues confined between activation of

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the VEGF receptor and VEGF gene transcription are the main focus of the new therapeutic tactics based on the use of VEGF antagonists. VEGF Trap, bevacizumab, ranibizumab, and pegaptanibare molecules that directly constrain the VEGF protein[5]. There are some signs and symptoms of diabetic macular oedema, such as; blurred vision, double vision, a sudden increase in eye floaters, seeing colours that look washed out or faded, and vision loss[6]. DME can occur at any stage in the course of diabetic retinopathy and it is the most frequent cause of visual impairment in the developing world. Treatment of DME was dramatically altered by the introduction of anti-VEGF (vascular endothelial growth factor) agent. Anti-VEGFs injections become the 1st line therapy for DR; they work against the vascular endothelial growth factors in the retina to control the growth of abnormal blood vessels from the choroid which is the main pathological problem of DR [7,8]The anti-VEGF treatments for DME currently approved by the United States Food and Drug Administration are ranibizumab (Lucentis; Genentech, South San Francisco, CA, USA), approved in August 2012, and aflibercept (Eylea; Regeneron Pharmaceuticals, Tarrytown, NY, USA), approved in July 2014. Bevacizumab (Avastin; Genentech) is widely used for the treatment of DME and is available at lower cost. Nowadays anti-VEGF therapy is an effective and powerful implement in the complications of uncontrolled diabetes mellitus which results in DME [9]. Our objective in this study was to evaluate the efficacy, safety, and injection frequency of anti-VEGF therapy (Bevacizumab) as used in clinical practice for the treatment of DME. The study aimed to evaluate the efficacy of different types of anti-VEGF therapy in the improvement of vision (BCVA) and the reduction of CMT.

Methods

A retrospective study was conducted in the Bashundhara Eye Hospital & Research Institute, a tertiary eye hospital, Dhaka, Bangladesh. Between January 2018 and March 2022, a total of 306 patients (a total of 368 eyes) having DME who received 3 anti-VEGF therapy (monthly interval due to reduced vision mean BCVA 20/40 & CMT 275µm were enrolled in this study. History and clinical examination findings were noted in a case record form. Data were collected from medical records at the time of the first to eleventh (as given monthly for follow up) anti-VEGF injection including demographics, medical and ophthalmic history, RBS, HbA1C, visual acuity (VA) by Snellen chart, Central macular thickness (CMT) by 3D optical coherence tomography (3D-OCT) and Intraocular pressure (IOP) by Goldmann Applanation Tonometer & Air Puff Tonometer. During the study period, patients were administered anti-VEGF (Bevacizumab) with the dose of 1.25mg/0.05ml (at one month interval).The information was kept confidential only to be used for the study purpose.

Inclusion criteria:

- Patients with avariable duration of DM
- Patients with the central macular thickness (CMT) >275 um
- Patients with reduced vision BCVA<20/40
- Patients having DME who received 3 anti-VEGF therapy
- DME with Previous or No H/O of administration of anti-VEGF therapy

Exclusion criteria:

- Patients with reduced vision due to HTN, macular scar, macular ischemia, ocular inflammation, CKD or another organ failure or severe anaemia
- Patients with DME received photocoagulation

Data Analysis:

The study coordinators performed random checks to verify data collection processes. Completed data forms were reviewed, edited, and processed for computer data entry. Statistical analyses were carried out by using the Statistical Package for Social Sciences version 26.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The quantitative observations will be indicated by frequencies and percentages.

Result

Total number of 306 patients (N=306) were included in this study. Their age range was 35-90

(mean age 58.83).Among them,117(38.22%) were males and 189(61.78%) were females.Two-fifth of the patients (123,40.86%) had glycosylated hemoglobin levels of 9 to 12%, and one-fourth of patients (77,25.48%) had glycosylated hemoglobin of more than 12%. Single eye was affected in 80% (244) of patients and only 20% (62) patients were affected by both eyes. 67.3% of patients had RBS level were less than 11.1mmol/L and 32.7% of patients had RBS were more than 11.1 mmol/L [Table-I]. Half of the study population (168,54.8%) were diagnosed with NPDR. 37.9% of patients were diagnosed with PDR [Table II]. Table III&IV shows improvement of mean BCVA &CMT level of all groups of patients after treatment with anti-VEGF which was significant ($p < 0.01$). The mean number of anti-VEGF injections administered in patients was 6±0.67 with a minimum of 3 anti-VEGF shots and a highest of 11 anti-VEGF shots. Around half of the study population (162,52.94%) were injected more than three injections and rest were injected thrice during the study period. Moreover, three (0.98%) patients were injected with 11 doses of anti-VEGF injection. [Figure2]. After application of intravitreal injection of Bevacizumab, visual acuity (BCVA) was improved in 297 (97.06%) patients. Remaining9 (2.94%) patients having uncontrolled DM were non-responsive to anti-VEGF therapy [Table V]. Before application of injections to both eyes, among 62 study populations, mean best corrected visual acuity (BCVA) were 20/200, 20/120, 20/80and after application of injection mean BCVA was improved to 20/120, 20/80, 20/60, respectively [Table VI]. Before the application of injection in single eye, among 244 patients, BCVA was 20/200,20/120, 20/60, 20/40, CF. After the application of injection, BCVA was improved and it was 20/120, 20/60, 20/40,20/30,20/200, respectively.[Table VII]. During the study period, 9 (2.94%) of patients were not responsive to anti-VEGF therapy. Among them, 6 patients (66.67%) had BCVA was counting figure (CF) and 3(33.33%) patients had hand movement (HM) [Table VIII]. The vision was improved in 139 (46.8%) patients after the application of 3consecutive injections. In addition, 158(53.2%) patients' vision was improved after administration of more than 3 anti-VEGF (Bevacizumab) injection [Table IX]. The mean central macular thickness (CMT) level of the study population was 450 ± 28.39 µm before the application of anti-VEGF therapy. The mean CMT level after 3 anti-VEGF therapy was 280± 17.02 µm, the mean CMT level after more than 3 anti-VEGF therapy was 250 ± 7.42 µm and the mean CMT level after anti-VEGF therapy for those whose vision was not improved was 350± 6.82 µm [Table X].

Table I : *Characteristics of the study population (N=306)*

Age		Mean Age 58.83±6.23 Maximum=90 Minimum=35		
		Number(N=306)		**Percentage (%)**
Gender	**Female**	189		61.78%
	Male	117		38.22%
Hypertension		164		53.84%
HbA_1C		8%	106	33.65%
		9-12%	123	40.86%
		>12%	77	25.48%
Affected eye		**Number(N=306)**		**Percentage (%)**
Single Eye		244		80%
BE		62		20%
RBS		<11.1mmol/L	100	67.3%
		>11.1mmol/L	206	32.7%

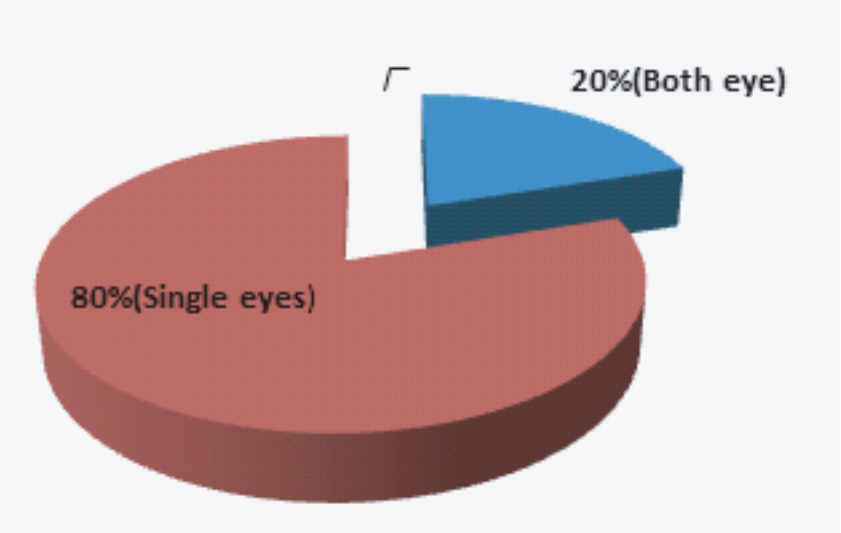

Fig 1: Distribution of Study Population Based on Affected Eye (N=306)

Table II : *Distribution of study population based on diagnosis (N=306)*

Diagnosis	Number(N=306)	Percentage (%)
ADED (Advanced Diabetic Eye Disease)	8	2.9%
NPDR (Non-Proliferative Diabetic Retinopathy)	168	54.9%
PDR (Proliferative Diabetic Retinopathy)	130	42.2%

Table III: *Comparison of BCVA Before& After treatment by intra-vitreal injection of Bevacizumab*

Anti-VEGF	Before treatment BCVA in Decimal		After treatment BCVA in Decimal		p-value
	Range	Mean, SD	Range	Mean, SD	
Bevaciizumab	20/300-20/60 (0.065-0.35)	0.2075, (0.05)	20/40-20/30 (0.50-0.65)	0.575, (0.09)	<0.001

***20/300 means counting finger (CF)**

Table IV: *Comparison of mean OCT level in µm Before & After treatment by Bevacizumab injection*

Anti-VEGF	Before treatment CMT(µm)		After treatment CMT(µm)		p-value
	Range	Mean, SD	Range	Mean, SD	
Bevaciizumab	295-761	675,(7.38)	161-223	192, (6.19)	<0.001

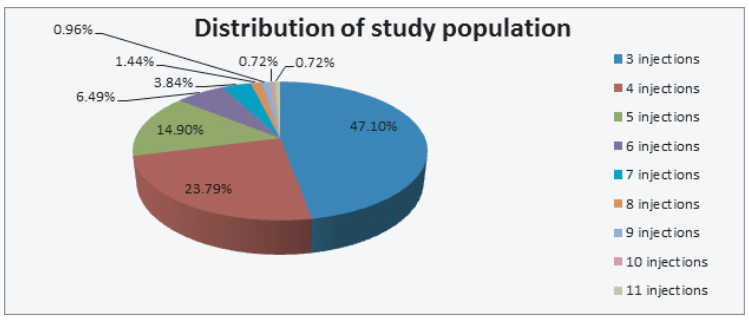

Fig 5: Distribution of study population based on number of injections applied (N=306)

Table V: *Distribution of study population based on Improvement of mean vision (N=306)*

Vision Improvement	Number(N=306)	Percentage (%)
Vision improved	297	97.06%
Vision Not Improved	9	2.94%

Table VI: *Distribution of study population based upon the improvement of eye vision after application of Bevacizumab therapy in BE, N=62*

Before application of injection	After application of 3 injection	Number	Percentage(%)	p -value
Mean Vision (BCVA)	**Mean Vision (BCVA)**			
20/200	20/120	20	32.26%	**<0.05**
20/120	20/80	32	51.61%	
20/80	20/60	10	16.13%	

Table VII: *Distribution of study population based on the improvement of eye vision after application of anti-VEGF (Bevacizumab) therapy, Single eye=235 (N: 244-9=235)*

Before Application of injection	After Application of injection	Number N=235(%)	p -value
20/200	20/120	105,44.2%	**<0.05**
20/120	20/60	71,30.4%	
20/60	20/40	31,12.7%	
20/40	20/30	25,10.15%	
CF	20/200	4,2.03%	

Table VIII: *Number of study population whose eye vision did not improve after application of Bevacizumab (N=9)*

	Number	Percentage (%)
Counting figure (CF)	6	66.67%
Hand movement (HM)	3	33.33%

Table IX: *Distribution of study population based on the improvement of mean vision & CMT level according to the number of Bevacizumab therapy (N=297)*

Improvement of vision according to anti-VEGF therapy	Number	%
After Administration of consecutive three anti-VEGF Therapy	139	46.8%
After Administration of more than three anti-VEGF Therapy	158	53.2%

Table X: *Distribution of study population based on mean CMT level (N=306)*

Mean CMT level of study population before anti-VEGF therapy (N=306)	450 ± 28.39µm
Mean CMT level of study population after three consecutive anti-VEGF therapy (n=144)	280± 17.02µm
Mean CMT level of study population after more than three anti-VEGF therapy (n=162)	250 ± 7.42µm
Mean CMT level of study population after anti-VEGF therapy (n=9)(No improvement)	350± 6.82µm

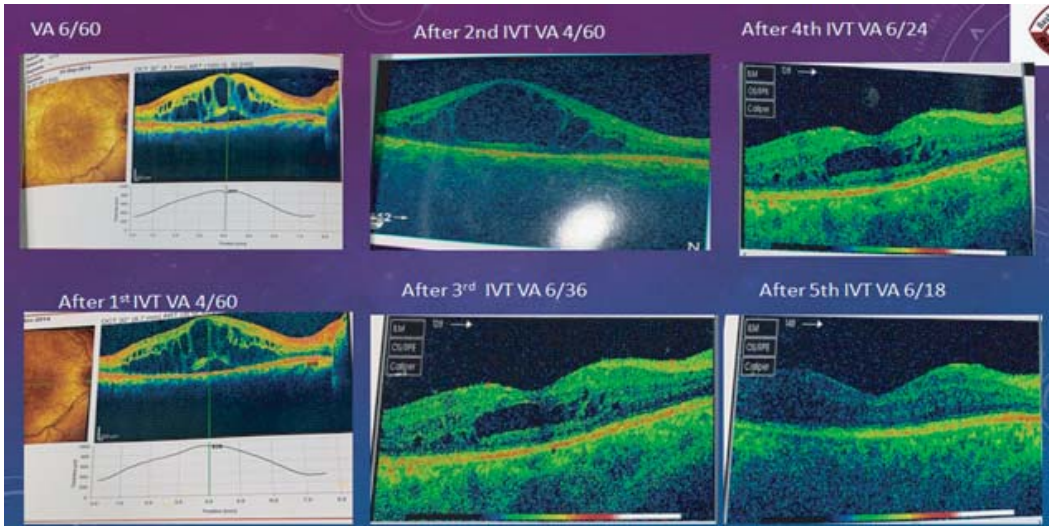

Figure 3: Figure showing diffuse retinal edema and presence of fluid in macula before Anti-VEGF injection (Bevacizumab) & a significant reduction of macular thickness after5 injections of Bevacizumab

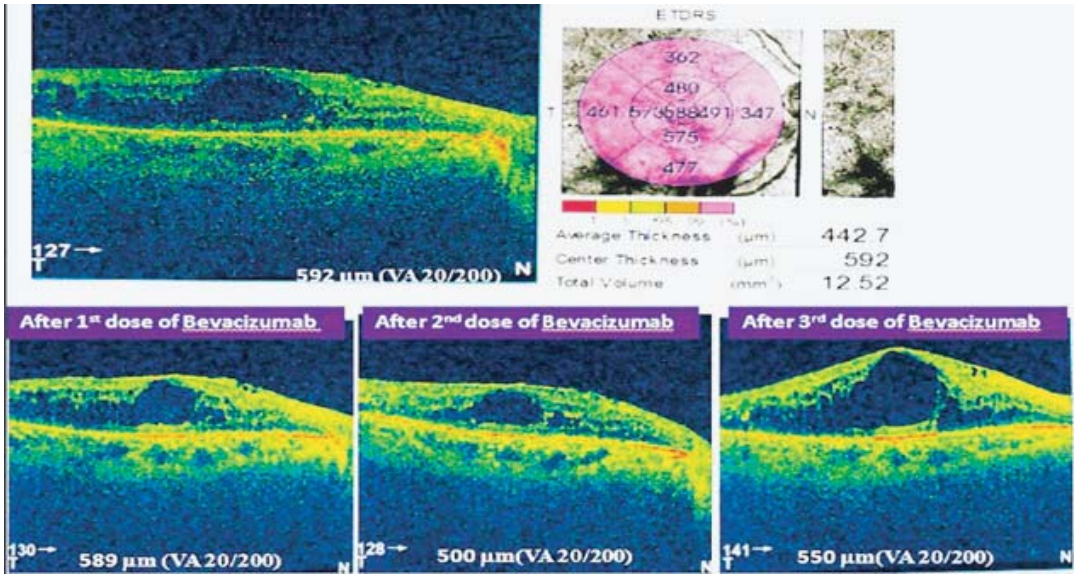

Figure 4: Figure showing diffuse retinal edema and presence of fluid in macula before Anti-VEGF injection (Bevacizumab) & no improvement of macular thickness after 3 injections of Bevacizumab

Discussion

Ocular complications are considered as most debilitating health consequences for adults with DM. In recent years, anti-VEGF therapy has turned up as a new standard of treatment for patients with DME. In current study, we tried to show the outcome of Bevacizumab (anti-VEGF agent) in DME patients. The DRCR.net Protocol T compared the three anti-VEGF agents for DME [21], on the possibility that one medication might be more effective in eyes with worse vision& higher macular thickness, possibly associated with higher VEGF levels and more active retinopathy. A pre-specified analysis was planned to compare results from two major subgroups: those with vision of 20/50 or worse and those with vision better than 20/50. The data from Protocol T showed that when the vision was better than 20/50, the efficacy of all three anti-VEGF medications for DME was similar. For severe DME with poor vision, the efficacy of Aflibercept is superior[33]. In this study, target population included according to inclusion criteria. So target BCVA of better than 20/40 and CMT level of<275µmwere considered as satisfactory level of improvement. In this study 306 patients were treated with intravitreal Bevacizumab injection for DME treatment. Recent studies denote that there are three anti-VEGF agents that could be useful for DME: bevacizumab, ranibizumab and aflibercept.[10] Bevacizumab is a full-length murine monoclonal anti-VEGF antibody that has been humanized, which has the distinct advantage of the lowest cost of the available therapies. Ranibizumab is an affinity-enhanced antibody fragment developed from bevacizumab. The Fab fragment lacks the Fc portion and is similar with monovalent binding to VEGF, as opposed to the bivalent binding of the bevacizumab antibody but with higher affinity.[11] In this study, 62 patients had DME in both eyes. Among them, the Visual Acuity (VA) of half of the patients' right eye was 20/120 and the left eye was 20/200before administration of anti-VEGF (Bevacizumab) therapy. They were improved to 20/60 and 20/120 respectively after injection. The recent clinical trials with anti-VEGF therapy have established similar improvement of vision for patients suffering from DME.[12]

In the present study, around half of the patients were applied anti-VEGF thrice in the study period and a significant improvement of vision was observed. A recent study reveals serum VEGF concentration after bevacizumab reduces plasma VEGF for up to 1 month after injection.[13] However, among the half-lives of three anti-VEGF, Bevacizumab has longer half life in vitreous .[14]

In the present study,9 (2.94%) patients were unresponsive to anti-VEGF therapy. It could be due to poor control of DM with high HbA1C>11% during the treatment period. Occasionally, patients are poorly responsive to anti-VEGF therapy. Pathophysiology of macular edema that is independent of VEGF should be investigated. As there is a significant inflammatory component in the etiology of macular edema, steroids have been extensively evaluated as a treatment option. Many inflammatory cytokines have been found to be elevated in patients with DR. [15]The mean CMT level of the study population was 450±28.39 µm before the application of anti-VEGF (Bevacizumab) therapy.

The mean CMT level after 3 intravitreal Bevacizumab injection was 280±17.02µm and the mean CMT level after more than 3 anti-VEGF therapy was 250.7±7.42µm. There was a study conducted among patients with DME at the Tokyo Medical University where the mean CMT of the study population was 514±SD µm and after one month of anti-VEGF therapy CMT reduced substantially to 299±SD µm. Although the study found no significant correlation between visual acuity and reduction of CMT after one month of anti-VEGF therapy[16].

Diabetic retinopathy is the leading cause of visual impairment and preventable blindness and represents a significant socioeconomic cost for health care systems worldwide. Hence, new approaches beyond current standards of diabetes care are needed. Based on the crucial pathogenic role of vascular endothelial growth factor (VEGF)

in the development of DME, intravitreal anti-VEGF agents have emerged as new treatments. The role of laser therapy along with anti-VEGF therapy is still ambiguous.[17] The anti-VEGF therapy is an important invention in the treatment of DME. More studies should be carried out to elucidate the long-term results and the safety profile.[18]

Treatment of DME with VEGF inhibitors is well tolerated in the clinical practice setting. In this study,we included Bevacizumab for intra-vitreal injections and compared the results. Though it is claimed that Ranibizumab & Aflibercept are superior to Bevacizumab.[19] Bevacizumab is more chosen by the patient due to it's cost effectiveness. Furthermore, there were few reports of adverse effects related to anti-VEGF therapy, although no reports of thromboembolic events related to anti-VEGF treatment. The lack of complications of anti-VEGF therapy also proved its favorable safety profiles in patients with DME[20]. Thus VEGF inhibitors have become the treatment of choice in DME because of their sanctuary as well as their effectiveness in reducing macular edema and improving visual acuity in patients with DME. Furthermore, anti-VEGF therapy has revolutionized the management of DME patients and provided a new standard of care, current study shows that there remains a significant number of patients unresponsive to anti-VEGF medications. The underlying reason for not responding to anti-VEGF agents because of the presence of a distinct number of mediators and signaling pathways in the retina. The promise of new, novel agents targeting other components of DME's pathogenesis would provide persistently improvements in patients' vision and quality of life. The expanding pharmacologic footsteps available in the retina subspecialty allow new prospects in DME patients.

Conclusion

The visual outcomes in this retrospective analysis appear to be comparable to previously reported outcomes in routine clinical practice. Our analysis provides some information about the effectiveness of anti-VEGF treatment in routine clinical practice atBashundhara Eye Hospital & Institute. Our study conclude Bevacizumab is not inferior to other practiced Anti-VEGF agents in the treatment of DME. Consecutive 5 anti-VEGF therapy for DME with reduced vision may be implemented in the management of patients in order to achieve better visual outcomes.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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External Resources

a. Pubmed/Medline (NLM)

b. Crossref (DOI)