Influence of Intravitreal Bevacizumab Therapy on the Patterns of Diabetic Maculopathy on Optical Coherence Tomography

Muhammad Atif Mian, FRCS* Mohamed Moemen AlReefy**

Objective: To evaluate the effect of intravitreal Bevacizumab (Avastin™) on optical coherence tomography (OCT) patterns of patients with different subtypes of diabetic macular edema (DME).

Setting: Ophthalmology Department, King Hamad University Hospital, Bahrain.

Design: A Retrospective Study.

Method: Seventy-one patients (142 eyes) with clinically significant diabetic macular edema who received intravitreal Bevacizumab therapy for six weeks were included in the study. Visual acuity and OCT patterns before and after receiving treatment were documented. Diabetic macular edema was subdivided into four groups: diffuse retinal thickening (DRT), cystoid macular edema (CME), pigment epithelial detachment (PED), and mixed features (both DRT and CME). Macular thickness, macular volume, and visual acuity before and after treatment were compared.

Result: Changes in patients' macular thickness and macular volume were significantly different for all four subtypes of DME (p=0.002, p=0.001) after treatment with Bevacizumab. Compared to CME and PED, eyes with DRT showed the greatest change in macular thickness, macular volume, and visual acuity after receiving intravitreal Bevacizumab. The change in visual acuity six weeks after treatment was not statistically significant (P= 0.61). Eyes affected with CME or PED were more likely to persist with chronic DME even after receiving treatment.

Conclusion: Patients with DRT had major benefit from intravitreal Bevacizumab. The study advocates the sub-classification of DME on OCT scans in order to predict patients' visual prognosis after receiving intravitreal Bevacizumab.

*   Consultant
    Department of Ophthalmology
    King Hamad University Hospital
    Kingdom of Bahrain
**Clinical Elective Student, RCSI-MUB
    Email: atifeye@hotmail.com

Diabetic retinopathy is the most common cause of blindness in the developed world[1]. Diabetic macular edema (DME) is a complication of diabetic retinopathy; it is defined as thickening of the central macular area of the retina. DME is typically seen within two optic disc diameters from the center of the macula[2,3]. The pathophysiology of DME starts with microvascular changes in

the retina, in which high serum glucose levels cause glucose to accumulate freely in the pericytes of retinal blood vessels. The conversion of glucose to sorbitol by aldose reductase results in osmotic damage to the retina. This change compromises the blood-retinal barrier, which leads to the leakage of fluid and protein into the retina, termed retinal edema[2-5]. DME is seen in patients with both proliferative and non-proliferative diabetic retinopathy.

The incidence of DM, particularly type two diabetes mellitus (T2DM), is rapidly increasing worldwide. In 2013, approximately 382 million people were affected with diabetes, 90% of which were T2DM. By 2035, this number is expected to reach 592 million people[3,7]. The International Diabetes Federation (IDF) listed five top ten countries, the highest prevalence of diabetes was in GCC countries[4,10]. Currently, Bahrain ranks fifth amongst GCC countries with 169,000 diabetics (13% of the population) between the ages of 29 and 70[7,10].

Recent studies revealed that patients who have been diabetic for more than ten years have 80% chance of acquiring diabetic retinopathy[5]. Despite this risk, recent studies have shown that up to 90% of patients with appropriate treatment for DM and close monitoring of glucose levels have a lower probability of suffering from retinal diabetic changes[8].

The enhancement of Ocular Coherence Tomography (OCT) has recently provided the identification of further macular pathologies. OCT is currently widely used for diagnostic confirmation and the subdivision of DME[3,4]. Based on morphological patterns seen using OCT, DME is subdivided into three types: cystoid macular edema (CME), pigment epithelial detachment (PED), and diffuse retinal thickening (DRT). Simultaneously, patients could present with mixed features of all three types.

Previously, the mainline treatment for DME was laser photocoagulation to the macula[6,9]. Although not being approved by the Food and Drug Administration (FDA), there is currently a significant off-label use of intravitreal Bevacizumab, an angiogenesis inhibitor to treat DME[5].

The relationship between different subtypes of DME seen on OCT and their visual prognosis after the treatment with Bevacizumab appears not to have been established.

The aim of this study is to evaluate the effectiveness of Bevacizumab injection in the subtypes of DME and to measure the macular parameters in OCT images six weeks after treatment.

METHOD

OCT images of 71 patients (142 eyes) with DME were treated with intravitreal Bevacizumab injections from June 2013 to September 2013 were reviewed.

The following personal characteristics were recorded: gender, age, duration of diabetes, history of hypertension and dyslipidemia, previous treatment with Bevacizumab, serum HbA1C, and the stage of diabetic retinopathy. Inclusion criteria were the following: Patients are affected with clinically significant DME as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS), have received only one Bevacizumab injection, and have not undergone any other

treatments for their DME. Patients are suffering from retinopathy due to pathologies other than diabetes and have received other modalities of treatment for DME were excluded[5].

The best corrected visual acuity (BCVA) for all 71 patients using previous ETDRS chart scores were recorded. Patients' slit lamp and 90-D lens examinations were considered to exclude other variables that could alter visual acuity such as cataract, glaucoma, and significant retinal damage or detachment. BCVA values of both eyes before and after treatment were compared and contrasted with the corresponding subtype of DME. To evaluate the values statistically, the VA scores were converted to logarithmic values of the minimal angle of resolution (logMAR).

OCT images before and after the intervention with Bevacizumab were evaluated. TOPCAN 3D OCT 2.0 was used under the '3D macular imaging' setting. The OCT software provided two quantitative results: central macular thickness (CMT) and total macular volume (TMV). According to recent studies, CMT is defined as the average retinal thickness within 1 mm from the fovea (the area of highest visual acuity); and TMV is the average thickness of the nine macular subfields seen on the OCT gridding pattern[6,10,11]. Patients with poor OCT images were excluded.

The morphological patterns of DME were subdivided into four[3,7,12]. Figure 1 reveals the OCT patterns of these subtypes. Cystoid macular edema (CME) presents with large intraretinal cysts with clearly demarcated septa between them and are not diffusely scattered across the macula, see figure 1A. Diffuse Retinal Thickening (DRT) shows small sponge-like spaces scattered diffusely across the macular area, as well as reduced intraretinal reflectivity, see figure 1B. Patients could also present with mixed features of both DRT and CME, see figure 1C. Pigment epithelial detachment (PED) portrays a clearly elevated retina, and an area of reduced reflectivity between the retina and pigment epithelium, marking epithelial detachment, see figure 1D.
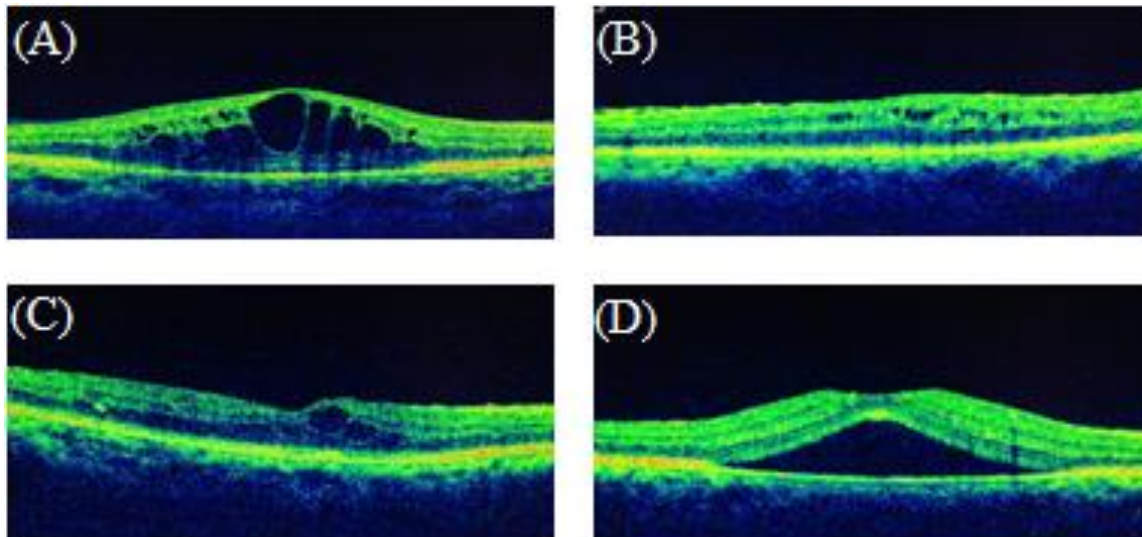

Figure 1: Subtypes of Diabetic Macular Edema (DMO)

Data were analyzed using Statistical Package for Social Sciences (SPSS) software version 19.0, and compared the results of the different subtypes of DME using analysis of variance (ANOVA); P value ≤0.05 was considered to be statistically significant.

Definition of Variables

Visual acuity was measured using ETDRS charts. According to the following best corrected visual acuity (BCVA) scores; patients' visual outcome was subcategorized as either being improved, worsened or unchanged.

- Improved BCVA: >15 letter increase
- Worsened: <15 letter decrease
- Unchanged: all other cases.

Central Macular Thickness (CMT) and Total Macular Volume (TMV): thickness of the retina within 1mm diameter from the fovea and the average thickness of the nine macular subfields, respectively. According to the guidelines in the ETDRS study, thickness >250 µms was identified as 'unimproved'[5,7,11].

RESULT

Seventy-four (58%) patients presented with cystoid macular edema. Two (3%) patients had pigment epithelial detachment which was the least common subtype, see figure 2.
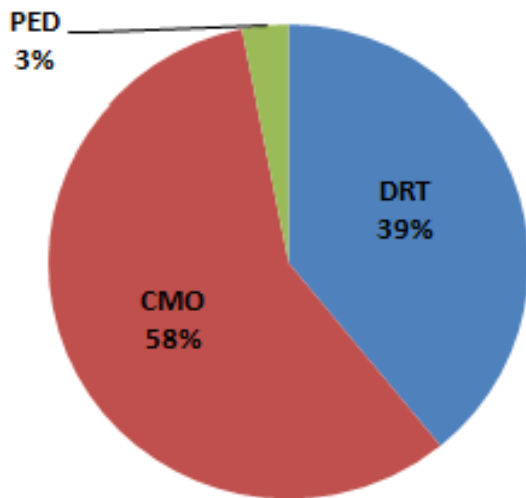

Figure 2: Patterns of Diabetic Macular Edema

Table 1 summarizes the details of 71 patients (142 eyes) affected with DME. The average age was 59.5 years. Forty-six (64.79%) males (92 eyes) and 25 (35.21%) females (50 eyes) were identified. The average duration of diabetes for all patients was 12.7 years. Ninety-four (66.2%) eyes had non-proliferative diabetic retinopathy (NPDR) while 48 (33.8%) eyes had proliferative diabetic retinopathy (PDR). One hundred eight (76.06%) eyes were affected with hypertension.

The average HbA1c was 7.7% for all four subtypes. P value was >0.05; therefore, there was no statistical significance.

Table 1: Details of 142 Eyes Affected with Diabetic Macular Edema

		Diffuse Retinal Thickening 50 (35.2%)	Cystoid Macular Edema 74 (52.1%)	Pigment Epithelial Detachment 4 (2.8%)	Mixed Features (CMO+DRT) 14 (9.9%)	Total 142 (100%)	P-Value
Gender	Male	20	21	1	5	46	
	Female	5	16	1	2	25	0.428
	Total	**25**	**37**	**2**	**7**	**71**	
Age (years)		58	59	55	66	59.5	0.735
Duration of Diabetes		12.0	11.1	9.3	18.4	12.7	0.192
Stage of DM	NPDR	32	54	2	6	94	
	PDR	18	20	2	8	48	0.837
	Total	**50**	**74**	**4**	**14**	**142**	
HbA1c (%)		7.9	7.6	7.9	7.5	7.7	0.247
Hypertension	Yes	36	58	4	10	108	
	No	14	16	0	4	34	0.848
	Total	**50**	**74**	**4**	**14**	**142**	

*NPDR: Non-Proliferative Diabetic Retinopathy, ** PDR: Proliferative Diabetic Retinopathy.

The influence of Bevacizumab injection therapy on CMT and TMV is summarized in table 2. The average initial CMT value (CMT_{IN}) for all four subtypes was 329.9 µm; the average initial TMV (TMV_{IN}) was 9.1 mm^3. The initial macular thickness and volume were significantly different between the four groups (P values ≤0.05). Patients with DRT had the lowest initial macular thickness (268.2 µm); while patients with PED initially had the highest (414.2 µm).

Table 2: Changes in Central Macular Thickness (CMT) and Total Macular Volume (TMV) after Bevacizumab Injection Therapy

	Diffuse Retinal Thickening	Cystoid Macular Edema	Pigment Epithelial Detachment	Mixed Features (CMO+DRT)	Total	P-Value
CMT_{IN} (µm)	268.2	347.1	414.2	290.2	329.9	0.01
CMT_F (µm)	234.1	340.3	390.1	276.1	310.1	0.01
Percent Change in CMT	12.7	2.1	5.8	5.4	6.5	0.002
Unimproved eyes (CMT>250	11	29	2	12	54	N/A
Improved eyes (CMT<250)	39	45	2	2	88	N/A
Total	**50**	**74**	**4**	**14**	**142**	
TMV_{IN} (mm^3)	8.8	8.4	10.1	8.9	9.1	0.004
TMV_F (mm^3)	7.8	7.8	9.7	8.1	8.4	0.1
Percent Change in TMV	11	9.4	3.9	8.1	8.1	0.001

CMT and TMV were measured for all patients six weeks after Bevacizumab injection therapy. The mean CMT for all subtypes after treatment (CMT_F) was 310 µm; no statistically significant difference (P=0.01). Compared to CME and PED, the eyes with DRT had 12% reduction in CMT. This reduction was statistically significant (P=0.002).

Fifty-four (76.06%) patients had persistent central macular thickness of >250 μms. In eyes with PED, 2 (50%) showed minimal or no improvement in CMT. In eyes with mixed features of both CME and DRT, 12 (85%) did not improve.

The average initial TMV (TMV_{IN}) after Bevacizumab injection was 9.1 mm^3. The final TMV (TMV_F) decreased to an average of 8.4 mm^3, which is a statistically significant reduction of 8.1% (P<0.001). Diffuse retinal thickening had a major change in TMV 11%, while pigment epithelial detachment had 3.9%.

Patients' visual acuity before and after the administration of Bevacizumab was compared, see table 3. Before initiating their treatment, $BCVA_{IN}$ of patients was 0.47 logMAR. Patients with DRT had a better BCVA than CME and PED; however, there was no statistical significance between the four groups (p=0.21).

Table 3: Changes in Best Corrected Visual (BCVA) after Bevacizumab Injection Therapy

	Diffuse Retinal Thickening	Cystoid Macular Edema	Pigment Epithelial Detachment	Mixed Features (CME+DRT)	Total	P-Value
$BCVA_{IN}$ (logMAR)	0.34	0.52	0.55	0.50	0.47	0.21
$BCVA_F$ (logMAR)	0.27	0.57	0.54	0.52	0.48	0.05
Change in BCVA (logMAR)	-0.07	0.05	-0.01	0.02	-0.01	0.61
Improved eyes	16	18	0	2	36	0.80
Unimproved eyes	26	44	2	4	76	N/A
Worsened eyes	8	12	2	8	30	N/A
Total	**50**	**74**	**4**	**14**	**142**	

Six weeks after therapy, the average BCVA ($BCVA_F$) was 0.48 logMAR. DRT showed the improvement in BCVA (-0.07) while CME and mixed features of CME and DRT revealed worsening of BCVA after treatment (+0.05 and +0.02, respectively). However, the change in BCVA after treatment was not statistically significant for all four groups (P<0.61).

The vision which has improved remained constant or decreased six weeks after Bevacizumab treatment is, see table 3. Thirty-six (25.35%) eyes showed improvement in BCVA scores. Seventy-six (53.52%) remained 'unchanged', and 30 (21.13%) eyes the BCVA became worse. There was no statistical significance in BCVA scores between the four groups (P=0.80).

DISCUSSION

Bevacizumab (Avastin™) has been widely used as a primary treatment for diabetic macular edema (DME).

Why certain subtypes respond better to Bevacizumab than others is not very clear; however, each subtype has a characteristic way of damaging the retina. For example, a recent histological report showed that one of the earliest signs of DME is damage to Müller cells (retinal glial cells) by intracytoplasmic swelling[11-14]. The sponge-like spaces seen in DRT are produced by this early mechanism. In CME, however, there are large cystic spaces which protrude into the outer retinal layers. This was due to chronic macular edema and, unlike DRT, CME causes liquefactive

necrosis of Müller cells[11-14]. In terms of PED, there is marked detachment of the PED; therefore, not only would patients have edema and swelling, but would also experience loss of retinal function[9,11-14]. This could explain why DRT demonstrated a relatively favorable response to anti-VEGF compared to CME and PED. Recent studies showed that intravitreal Bevacizumab at doses of 1.25 to 2.5 mg is effective for the treatment of DME for periods up to 6 months and is effective for patients who have not responded to other modalities of treatment such as photocoagulation and vitrectomy[8,10,11-15].

The study had few limitations. The study was retrospective, which has an increasing probability of bias. No control group was recruited for the study. The fact that OCT images were taken manually could decrease the accuracy of results from patient to patient due to factors such as movement and incorrect boundary measurements. In addition, the number of patients with pigment epithelial detachment was very small, and the timeframe given for follow-up was relatively short. The study sample was relatively small compared to Bahrain's diabetic population and the number of patients registered at other hospitals in the Kingdom.

It is recommended that further prospective randomized controlled multicentric trial should be performed with a follow-up period of at least six months to attain more accurate results.

CONCLUSION

The study revealed that diabetics with diffuse retinal thickening would benefit the most from intravitreal Bevacizumab therapy during the first six weeks. Cystoid macular edema was the most prevalent subtype of DME, while pigment epithelial detachment was the least. Compared to cystoid macular edema and pigment epithelial detachment, those with diffuse retinal thickening had the greatest change in both OCT patterns and best corrected visual acuity after treatment with Bevacizumab.

REFERENCES

1. Kertes PJ, Johnson TM. Evidence Based Eye Care, 1st ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007: 2.

2. Wild S, Roglic G, Green A, et al. Global Prevalence of Diabetes: Estimates for the Year 2000 and Projections for 2030. Diabetes Care. 2004; 27(5):1047-53.
3. Ford JA, Lois N, Royle P, et al. Current Treatments in Diabetic Macular Oedema: Systematic Review and Meta-Analysis. BMJ Open 2013; 3(3) pii: e002269.
4. O'Malley PG. Comparative Effectiveness of Anti-Growth Factor Therapies for Diabetic Macular Edema: Summary of Primary Findings and Conclusions. Arch Intern Med. 2012; 172(13):1014-5.
5. Early Photocoagulation for Diabetic Retinopathy. ETDRS Report Number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1991; 98(5 Suppl):766-85.
6. Alhyas L, McKay A, Balasanthiran A, et al. Quality of Type 2 Diabetes Management in the States of the Co-Operation Council for the Arab States of the Gulf: A Systematic Review. Plos one 2011; 8(e22186).
7. Arevalo JF, Guerra J, Mercado H, et al. Primary Intravitreal Bevacizumab (Avastin) for Diabetic Macular Edema: Results from the Pan-American Collaborative Retina Study Group at 6-Month Follow-Up. Ophthalmology 2007; 114(4):743-50.
8. Fraser-Bell S, Kaines A, Hykin PG. Update on Treatments for Diabetic Macular Edema. Curr Opin Ophthalmol 2008; 19(3):185-9.
9. Williams R, Airey M, Baxter H, et al. Epidemiology of Diabetic Retinopathy and Macular Oedema: A Systematic Review. Eye (Lond) 2004; 18(10):963-83.
10. Causes and Risk Factors. Diabetic Retinopathy. United States National Library of Medicine. Available at: https://www.nei.nih.gov/health/diabetic/retinopathy. Accessed on 15.32014.
11. Mohamed Q, Gillies MC, Wong TY. Management of Diabetic Retinopathy: A Systematic Review. JAMA 2007; 298(8):902-16.
12. Diabetic retinopathy. Mayo Clinic. Available at: http://www.mayoclinic.org/diseases-conditions/diabetic-retinopathy/basics/definition/con-20023311. Accessed on 6.3.2014.
13. Avery RL, Pearlman J, Pieramici DJ, et al. Intravitreal Bevacizumab (Avastin) in the Treatment of Proliferative Diabetic Retinopathy. Ophthalmology 2006; 113(10):1695.e1-15.
14. Arevalo, JF, Maia M, Flynn HW, et al. Tractional Retinal Detachment Following Intravitreal Bevacizumab (Avastin) in Patients with Severe Proliferative Diabetic Retinopathy. Br J Ophthalmol 2008; 92:2 213-216.
15. Avery RL. Regression of Retinal and Iris Neovascularization after Intravitreal Bevacizumab (Avastin) Treatment. Retina 2006; 26(3):352-4.