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Ranibizumab Response in Diabetic Macular Edema at Mansoura Ophthalmology Center

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Short tile: Ranibizumab Response in DME at MOC

Abstract

Purpose: Diabetic macular edema (DME) is a complicated disease due to a multifactorial process comprising the breakdown of the blood retinal barrier with a subsequent fluid accumulation in the macula. Treatment of DME depends recently on more successful therapies such as anti-vascular endothelial growth factor (VEGF) therapies that could stabilize or improve vision in several cases. Ranibizumab has been submitted for approval as a treatment of visual impairment owing to DME.

Objective: To assess the response of intravitreal injection (IVI) of ranibizumab in DME at Mansoura ophthalmology center.

Patients and methods: This were a prospective study carried out on a total of 50 diabetic cases with DME. Full history was taken from included cases and full ophthalmological examination was conducted in addition to evaluation of the macular retinal maps using optical coherence tomography (OCT) (Spectral domain OCT 2000). Three monthly consecutive intravitreal injections of anti-VEGF of ranibizumab at a dosage of 0.5mg/0.05 ml were administered to all the cases.

Results: There was highly statistically significant improvement in the visual acuity (VA) and highly statistically significant reduction in the macular thickness in the included cases after one month and after three months as compared with the pretreatment value ($P<0.001$). The degree of diabetic control didn't appear to affect the change of the macular thickness.

Conclusion: The intravitreal ranibizumab injection effectively decreased macular thickness and improved VA. The structural and functional effects of ranibizumab appeared as early as after 1 month of treatment and maintained at 3 months following treatment.

Key words: Diabetes, Macular edema, Optical coherence tomography, Macular thickness.

INTRODUCTION:

Diabetic retinopathy (DR) is considered the main etiology of blindness among working-age adults, and DME is the main reason for vision loss related to DR[1].

Retinal oedema is responsible for retinal micro-structural alterations, retinal atrophy of photoreceptors and ganglion cell disorders[2]. In addition, it might be considered consensual that the best improvements in VA could be accomplished when retinal oedema is managed. In the context of a chronic and progressive disease, DME has to be faced as a state to control as effectively and rapidly as possible[3].

The more increase in duration of diabetes mellitus (DM) and the higher level of glycosylated hemoglobin (HbA1c) are the main predisposing factors for DME development in diabetic cases[4].

Of note, VEGF was reported to be responsible for the abnormal vascular permeability in DME[5]. The DME treatment has been shifted from the laser photocoagulation to anti-VEGF therapy[6].

The advantages of anti-VEGF therapy in decreasing DME and improving patient's vision have been reported in many studies[7-10].

Ranibizumab, in addition to aflibercept, have been reported as the first line therapies among the other anti-VEGF[11-13].

There are several data demonstrating the efficiency of ranibizumab in treatment of patients with DME[14-16]. On the other hand, there are studies that revealed poor response of some patients to anti-VEGF therapies even after 3 or more injections[17, 18].

PATIENTS AND METHODS

This is a prospective and interventional study carried out at Mansoura ophthalmology center, Mansoura University, Mansoura, Egypt from January 2020 to December 2020.

This study included 50 diabetic patients with DME (central macular thickness > 300 μm) from both genders. The cases with the following conditions were excluded; Patients with history of previous of IVI of anti-VEGF and steroids with duration less than one year, history of Grid or focal macular laser and history of pars plana vitrectomy.

The current study was submitted for approval from the institutional review board of Mansoura Faculty of Medicine and obtaining an informed written consent from the participants (code number MS.19.10.860), date (3\12\2019).

All cases were subjected to complete history taking and through full general examination.

Full detailed ophthalmic examination was performed for all the cases comprising assessment of the visual acuity (VA) using Landolt's VA chart and after that transformed for statistical analysis to Log MAR. The objective refraction was done using a streak retinoscopy, followed by subjective refraction with trial frame and Snellen eye chart placed at 6-M distance.

Slit lamp biomicroscopy (Haag Streit BP 900) (Haag-Streit, Koeniz, Switzerland) was utilized to evaluate cornealtransparency, anterior chamber for depth and regularity, pupil shape, size, regularity and reactivity, state of the lens and complications of DM which include recurrent stye, xanthelasma, accelerated senile cataract, rubeosisiridis.

Posterior segment examination was conducted by utilizing indirect ophthalmoscope and slit lamp biomicroscopy with auxiliary contact lens.

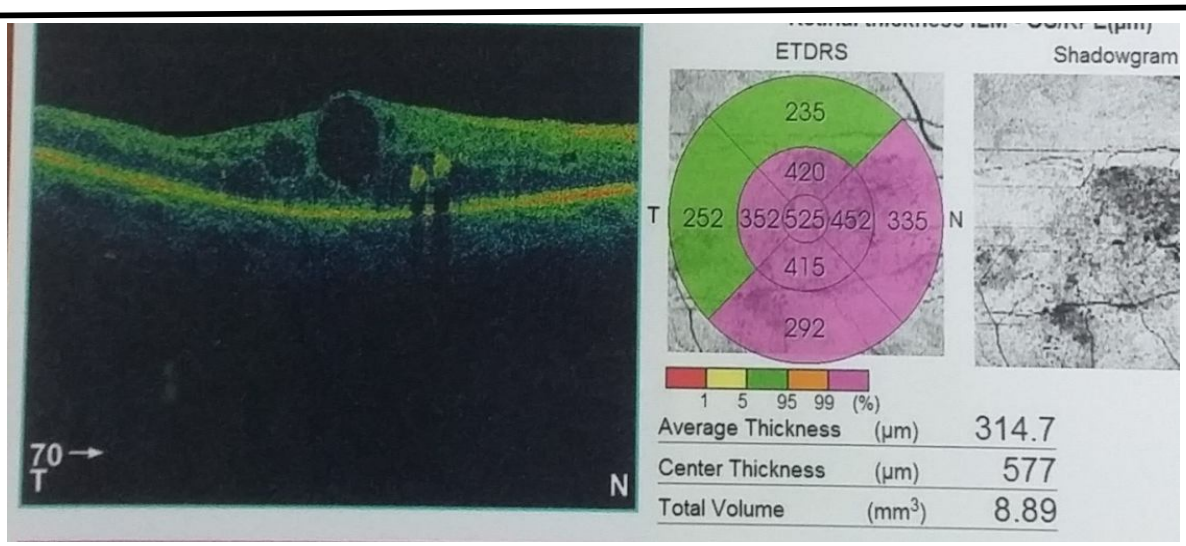
Optical coherence tomography Spectral domain (SD-OCT) 2000 [Topcon, Inc., Paramus, NJ, USA] was used to assess the state of the retina and macula (Fig. 1).

Figure 1: Topcon3D OCT

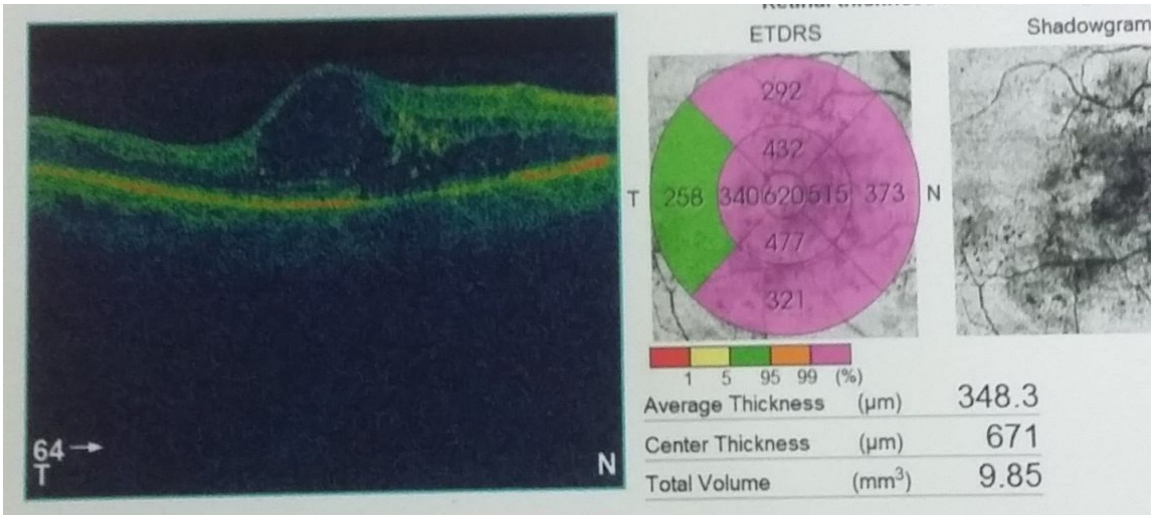
The following laboratory investigations were done for whole the cases (HBA1C, lipid profile and serum creatinine). Entire blood samples were divided into two aliquots: the first part was collected in a vacationer tube containing Na2-EDTA for the assay of HbA1c; the second was collected in a plain vacationer tube and centrifuged (3000 r.p.m) for serum preparation.

Three consecutive monthly IVI of anti-VEGF of ranibizumab (Lucentis; Novartis, Basel, Switzerland) at a dosage of 0.5mg/0.05ml were administered in a sterile manner using a 30-G needle toward the center of the vitreous at 4mm in phakic or 3.5mm in pseudo phakic eyes and inferotemporally from the limbus.

The cases were assessed at 1 month & 3 months regarding the VA and macular thickness. Example for oct of a case before and after IVI injection of ranibizumab (Fig. 2).



A) OCT scan and colour thickness map of first IVI injection of ranibizumab



B) OCT scan and colour thickness map of second IVI injection of ranibizumab

Fig. 2: Example for oct of a case before and after IVI injection of ranibizumab.

Statistical analysis

Data analysis was performed by Statistical Package for the Social Sciences (SPSS 26.0, IBM/SPSS Inc., Chicago, IL) software. Categorical data were expressed as frequencies and percentages (%) while in the quantitative data, we used mean and standard deviations (SD) as well as median (range).

For quantitative data, independent-Samples t-test and Mann-Whitney U test were utilized to compare 2 groups of parametric and non-parametric quantitative data correspondingly.

For comparing the quantitative data at two time points, we used paired samples t-test and Wilcox on signed rank test for parametric and non-parametric data correspondingly. For comparing the quantitative data at three time points, we used repeated measures ANOVA test and Friedman's test for parametric and non-parametric data correspondingly.

Pearson's correlation coefficient and spearman's correlation coefficient were utilized to test the association between two quantitative parametric and non-parametric variables correspondingly. The positive coefficient indicates direct correlation while negative coefficient indicates inverse correlation with increasing the strength of correlation with approximating to +1 and -1. Probability (p value) ≤ 0.05 was considered to be statistically significant.

RESULTS

As demonstrated in table (1), The mean age in the cases was 56.92 ± 7.27 years. There is 28 males (56%) and 22 females (44%). The mean duration of DM was 14.15 ± 4.41. There were 48 cases (96%) with IDDM and 2 cases (4%) with NIDDM. The mean HBA1C was 9.12 ± 2.04.

There were 21 cases (42%) with no Hypertension and 29 cases (58%) represented with Hypertension. There were 48

cases (96%) without renal affection and only 2 affected (4%). There were 45 cases (90%) with no Hepatitis C virus and 5 cases with HCV (10%). There were 43 cases (86%) without previous surgery and only 7 cases (14%) with previous surgery. The mean Triglycerides level was 175.19 ± 86.01, the mean cholesterol was 221 ± 53.58, the mean Low density lipoprotein level LDL was 145.39 ± 27.27 and High-density lipoprotein level HDL was 49 ± 15.46.

Table (1): Demographic, medical history, surgical history and laboratory data in study cases

		Total number=30		
		mean ± SD	**Median**	**Range**
Age/years		56.92 ± 7.27	57	(44-74)
Sex	**Males**		28 (56%)	
	Females		22 (44%)	
Duration of DM (Years)		14.15 ± 4.41	14	(7-20)
Type of DM	IDDM		48 (96%)	
	NIDDM		2 (4%)	
Medical and surgical history				
	HTN		29 (58%)	
	Renal affection		2 (4%)	
	HCV		5 (10%)	
	Previous surgery		7 (14%)	
Laboratory data				
HbA1C (%)		9.12 ± 2.04	8.73	(5.72-13.2)
TGs (mg/dl)		175.19 ± 86.01	151	(80-415)
Cholesterol (mg/dl)		221 ± 53.58	219	(135-323)
LDL (mg/dl)		145.39 ± 27.27	149	(100-184)
HDL (mg/dl)		49 ± 15.46	48	(25-75)

As demonstrated in table (2), The mean VA before treatment was 1.22 ± 0.36, at 1 month was 1.03 ± 0.31 and at 3 months was 0.86 ± 0.25. There was a highly statistically significant improvement in the VA in the included cases after one month and after three months as compared with before treatment value ($p<0.001$). Also, there was a highly statistically significant improvement in the VA after three months of treatment as compared with at 1 month value ($p<0.001$).

The mean Macular thickness before treatment was 467.39 ± 120.04, at 1 month was 362.89 ± 130.33 and at 3 months was 292.83 ± 80.88. There was a highly statistically significant decrease in the macular thickness in the included cases after one month and after three months as compared with before treatment value ($p<0.001$). also, there was a highly statistically significant decrease in the macular thickness after three months of treatment as compared with at 1 month value ($p<0.001$).

Table (2): Analysis of Visual acuity and Macular thickness (µm) in the cases of the study along the duration of follow up

Variables	Follow up			Test of significance
	Before treatment (N=50)	At 1 month (N=50)	At 3 Months (N=50)	
Visual acuity (VA)				
Mean ± SD	1.22 ± 0.36	1.03 ± 0.31	0.86 ± 0.25	P < 0.001*
		(-51.9:0)	(-62.58:0)	P1< 0.001*
Percent of change				P2 < 0.001*
				P3 < 0.001*
Macular thickness (µm)				
Mean ± SD	467.39 ± 120.04	362.89 ± 130.33	292.83 ± 80.88	P < 0.001*
		(-54.42:0)	**(-56.51: -17.14)**	P1 < 0.001*
Percent of change				P2 < 0.001*
				P3 < 0.001*

* statistically significant if P ≤0.05

P1: Significance between before treatment value and value at 1 month

P2: Significance between before treatment value and value at ٣ months

P3: Significance between value at 1 month and value at ٣ months

According to the degree of diabetes control, there was 8 cases (16%) with controlled diabetes and there were 42 cases (84%) with uncontrolled diabetes. As demonstrated in table (3), there was no statistically significant difference in the percent of change of macular thickness at 1 moth and 3 months between the cases with controlled versus uncontrolled diabetes.

Table (3): Relation between diabetic control and change of macular thickness

Items	Controlled n= 8	Uncontrolled n= 42	P value
Percent of change of macular thickness at 1 month			
Mean ± SD	-16.26 ± 9.44	-23.74 ± 17.44	**0.427**
Range	(-23.74:-4.88)	(-54.42:0)	
Percent of change of macular thickness at 3 months			
Mean ± SD	**-42.87 ± 3.75**	-36.26 ± 11.93	**0.124**
Range	(-44.89:-36.8)	(-56.51:-17.14)	

Table (4) shows that, there was a statistically significant positive correlation between change of VA with cholesterol and change of macular thickness.

Table (4): Correlation between change of VA and other factors in the study

Variables	change of VA at 3 months (Log mar)	
	r	P
Age	0.032	0.825
Duration of DM	- 0.256	0.111
HBA1C	- 0.145	0.330
TGs	0.060	0.726
Cholesterol	0.419	0.011*
LDL	- 0.268	0.168
HDL	0.105	0.649
Change of Macular thickness	0.450	0.001*

DISCUSSION:

This study was conducted to evaluate response of IVI of ranibizumab in DME at Mansoura ophthalmology center. The study comprised 50 diabetic cases with DME who were recruited along a period of one year.

The mean age in the cases was 56.92 ± 7.27 years. There is 28 males (56%) and 22 females (44%).

Prevalence of either males or females showed great differences between the different studies. Females constituted nearly about two thirds (64%) of diabetic population, in previous epidemiological researches conducted in Egypt [19, 20].

However, gender wasn't demonstrated to be asignificant predisposing factor for developing DR in the majority of the previous researches[20-23]. Moreover, certain researches demonstrated that; males were more liable for DR development in comparison with females, as in UAE[24] and Oman[25].

In the current study, the average duration of DM was 14.15 ± 4.41. There were 48 cases (96%) with IDDM and 2 cases (4%) with NIDDM. The mean HBA1C was 9.12 ± 2.04.

In the same line, comparable duration was recorded by Tang and his colleagues who have demonstrated that the duration of DM among their patients was 13.5 (SD 9.37) years[26].

This was shorter than the duration recorded in a research carried out in Saudi Arabia where the average age of onset and average duration of DM were 43.91 and 13.4 years, correspondingly[27].

The discrepancies among researches could be explained by difference in inclusion criteria of the included patients.

In the current study, there was a highly statistically significant drop in the VA and macular thickness in the included cases after one month and after three months as compared with before treatment value ($p<0.001$). also, there was a highly statistically significant reduction in the VA and macular thickness after three months of treatment as compared with at 1 month value ($p<0.001$)

The current results came in accordance with Sarhan et al. (2019) who observed that ranibizumab significantly improved BCVA and CMT after three consecutive monthly intravitreal injections, and this significance was maintained up to three months following the last injection[28].

The results of our study concerning the relationship between VA or macular thickness and intravitreal ranibizumab was also confirmed in the study[11]

Comparable outcomes were defined by Ashraf and his colleagues who recorded that in spite of a significant reduction in CFT following the switch to ranibizumab in eyes with DME refractory to bevacizumab[29].

Within the same context, Lai et al. (2020) have demonstrated that IVI of ranibizumab was demonstrated to be associated with a significant improvement in BCVA and reduction of the CFT over one year[5].

In a recent meta-analysis, there was a significant elevation in values in comparison with the pretreatment value. As regards whole study types, the largest total increase from basal value was noticed at 36 months, with a change in BVCA of 10 letters. The authors also reported that ranibizumab had a significant impact on CFT at all-time points, demonstrating a significant reduction in comparison with the basal value. In the context of all study types, the average CFT decrease was 159µm at 12 months, 135µm at 24 months, and 223µm at 36 months[30].

The REFINE study demonstrated anaveragedrop of 146.5µm for CFT after one year of therapy under "3 + PRN" regimen[31]. The RISE and RIDE study recorded an average reduction of 249.3µm for CFT following monthly IVI of ranibizumab for one year[32] where as Nepomuceno and his colleagues have recorded an average reduction of 126µm for CFT under monthly IVI of ranibizumab[33].

The current study demonstrated that, there was a statistically significant positive association between change of VA with cholesterol and change of macular thickness.

Prior researches recorded that VA improvement from basal level was demonstrated to be accompanied by reductions in the CMT from basal value[34].

Our results were also in accordance with Sarhan et al. (2019) who demonstrated that there was a significant ($P<0.01$) correlation between the average change in CMT of all study stages and the average change in BCVA. One month after each injection, BCVA improved significantly, as a result of reduced macular edema and vascular leakage.

Our results also came in accordance with Minami et al. (2017) who demonstrated that there was a significant ($p < 0.05$) correlation between the Δ CMT-1w and ΔVA-1w in the present study. Further researches with a large sample size are required to verify the association between the improvements in BCVA and improvements in CMT[35].

These outcomes are in accordance with prior studies' outcomes in terms of the correlation between CMT and VA after ranibizumab[36].

Browning and his colleagues have demonstrated that, although there was a significant correlation between VA and CMT, there was a great change in VA at any given retinal thickness, and OCT measurement solely mightn't be a nice replacement for VA as the primary result in researches of DME. OCT could only record the degree of oedema; the duration of oedema and the damage to cells cannot be assessed. Further study with more functional macular tests is warranted to study the relations between VA, macular state, and CMT[37].

In the current study, the most significant correlation among the three injections was observed between the baseline CMT and at 1 month after the first injection. These results were in accordance with Sarhan et al. (2019).

It was recorded that the basal value of CMT may predict the structural outcomes following IVI of ranibizumab[38]. The most significant correlation among the three injections, also, was observed between the basal value of BCVA and at 1 month. As formerly recorded, the basal value of BCVA might predict the functional outcomes following IVI ranibizumab therapy[39].

Taken together, the study reported that measuring the efficiency as early as one month after an IVI of ranibizumab in cases with DME may be predictive of the structural and functional effects of the IVI of ranibizumab in addition to the prediction from the basal value of CMT and BCVA.

In addition, a less CMT and BCVA effect was observed at three months than at one month. This recommends that other inflammatory or angiogenic cytokines down the cascade at a later phase might participate in the pharmacodynamics of ranibizumab[11].

Although several studied have demonstrated that; there was a significant association between BCVA letter scores and CFT in DME cases managed with anti-VEGF therapy, such correlation is only moderate throughout the initial year of therapy[40, 41], implying that loss of VA is likely multifactorial and might depend mainly on the disturbance of the retinal architecture or direct photoreceptor damage owing to longstanding oedema or other factors[42].

Certain researches have demonstrated that patients accomplish brilliant anatomical outcomes with anti-VEGF treatment but don't accomplish corresponding functional improvement. In addition, disorganization of the inner retinal layers, determined by SD-OCT, is accompanied by a worse baseline BCVA and less promising outcomes[43].

On the other hand, in certain cases with persistent DME, BCVA might be kept or improved after the therapy. Actually, in cases with DME, marked diurnal alterations we rerecorded in retinal thickness measurements, that might be, partially, owing to factors which include alterations in blood pressure as well as retinal metabolism[44, 45].

The present study had certain limitations. First, the relatively small sample size to carry out a subgroup analysis. Thus, further major clinical research is required. Second, the duration of follow up was short, thus additional research with a long follow up period is essential to determine whether or not the short-term effects of an IVR injection on the BCVA and CMT are associated with the long-term effects of the IVR injection on the BCVA. Third, the present study had no control group.

The effects of the natural disease course or previous treatments on the current results can't be excluded. In the present study, we couldn't assess the effect of circadian fluctuation, the reproducibility and alterations in the retinal thickness measurements in healthy individuals and patients. Further clinical study that comprises a control group and repeated measurements is required.

The current study had some limitations. First, the number of patients in this case series was too small to perform a subgroup analysis. Another larger clinical study is needed. Second, the current follow-up period was short and another clinical study with a long follow-up period is necessary to determine whether or not the short-term effects of an IVR injection on the BCVA and CMT are correlated with the long-term effects of the IVR injection on the BCVA. Third, the current study had no control group.

It could not exclude the influences of the natural disease course or previous treatments on the current results. In the current study, we could not evaluate the effect of circadian fluctuation and the reproducibility and variations in the retinal thickness measurements in both healthy subjects and patients. Another clinical study that includes a control group and repeated measurements is needed.

Conclusion:

The current study recommended that intravitreal ranibizumab effectively decreased macular thickness and improved VA. The results were maintained up to 3 months following the last dosage of ranibizumab.Structural and functional effects of intravitreal ranibizumab injection might be detectable as early as one month following the therapy.The degree of diabetic control didn't affect the degree of change of visual acuity and macular thickness.

Recommendations: Strict and regular control and follow up of cases with diabetes to prevent the occurrence of associated complications especially diabetic retinopathy.

Further studies should be performed including larger number of patients from more than a single center.

Control of modifiable risk factors could have a positive impact on progression of DR and on DME onset. Kawasaki R et al., observed an association between lipid-lowering medication and a decrease of DR and its complications. Furthermore, an association between statins medication and vitamin C (as an antioxidant agent) supplementation could have a synergistic role in lowering DME onset and DR progression.

all persons with diabetes receive at least yearly dilated eye examinations and are offered appropriate treatment when indicated.

DATA AVAILABILITY

All data are included in this article.

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None

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Ethics declarations

Conflict of interest

Roaa N. Elbeheiri, Sahar M. Eltarshouby, Hossameldin Y. Abouelkheir, Amr M. Abdelkader all authors have no conflicts of interest that are directly relevant to the content of this review.

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