Factors Affecting Outcome of Anti VEGF in Management of Diabetic Macular Edema

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Abstract: Purpose: To evaluate Factors affecting outcome of intravitreal Anti VEGF (Ranibizumab) in the management of Diabetic Macular Oedema. **Methodology:** Twenty eyes of twenty patients were enrolled in the study. The patients received three monthly intra vitreal injection of 0.5mg /0.05ml ranibizumab. **Inclusion criteria**; Patients with diffuse diabetic macular edema with central macular thickness (CMT) >300um. **Exclusion criteria**; proliferative diabetic retinopathy, Cases with any macular disease other than diabetic maculopathy, Cases with history of cataract surgery within 12 months, Cases with significant cataract which interferes with OCT. **Results:** The mean CMT changed from **474.30 ± 120.97**um (319-680) at base line to **389.55 ± 85.99**um (287-600) at 6months. The mean BCVA (log MAR) changed from **0.97 ± 0.19** at base line to **0.79 ± 0.24** at 6months. Cases with interrupted ellipsoid zone showed poor functional response. HbA1c showed no correlation with the response. **Conclusion**: Ranibizumab is effective in treating DME. Outer retinal integrity in OCT is a predictor for response to treatment.

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1. Introduction:

Diabetic retinopathy (DR) is a leading cause of blindness in adults and diabetic macular edema (DME) is the most common cause of visual loss in patients with diabetes mellitus (DM) (**Coscas et al. 2010**).

The pathogenesis of DME has not been fully elucidated since it is caused by complex pathological process with many contributing factors. Dysfunction of the inner and outer retinal barriers leads to accumulation of sub- and intra-retinal fluid. Vascular endothelial growth factor (VEGF) has generally been accepted as the main factor that disrupts the inner blood-retinal barrier (BRB) function, making it an important target for pharmaceutical intervention **(Zhang et al., 2008**).

Breakdown of the outer, especially the inner retinal blood barrier is an early event in the pathogenesis of DME **(Zhang et al., 2008**). Hypoxia, ischemia, oxygen-free radicals and inflammatory mediators are all involved in the breakdown retinal blood barrier (BRB). Muller cell, pericyte and glial cell dysfunction combined with vitreous changes are involved in the occurrence and development of macular edema. Chronic hyperglycemia, hypertension and high cholesterol are also important factors related to the incidence of macular edema **(Bhagat et al., 2009**).

Different treatments modalities for DME have been used, e.g., grid laser photocoagulation, intravitreal injection of triamcinolone acetonide (IVTA), posterior sub-Tenon's capsule triamcinolone acetonide (STTA) injection, pars plana vitrectomy (PPV), subthreshold micropulse diode laser photocoagulation and intravitreal injection of anti-vascular endothelial growth factor (VEGF) drugs **(DRCR.net 2012)**.

Nowadays intravitreal injection of anti-vascular endothelial growth factor (VEGF) is considered the gold standard for center involving DME. Recent studies showed that diabetic macular edema persists in 25%–64%of injected eyes in spite of repeated injections **(DRCR.net 2012, DRCR.net 2015).**

Ranibizumab is an intravitreal anti-VEGF agent that is FDA approved for the treatment of wet AMD, and DME **(Prünte et al., 2015).** Several studies have reported the superiority of RBZ as compared to laser treatment.

Identifying risk factors that affect the success or failure of treatment could help investigators to make informed decisions as to which patients should be treated with intravitreal ranibizumab. Therefore, we are presenting analyses of twenty eyes which received intravitreal ranibizumab to study factors affecting outcome of treatment.

2. Patients and Methods:

This is a prospective interventional study, conducted between May 2015 and March 2017. The study protocol was approved by the ethical committee of Fayoum University Hospitals. Every patient gave a written informed consent to participate in the study.

Study population

Twenty eyes of twenty patients which met the inclusion criteria were enrolled in the study. The patients received three monthly intra vitreal injection of 0.5mg /0.05ml ranibizumab ((Lucentis; Genentech, South San Francisco, CA).

Inclusion-criteria

Patients with diffuse diabetic macular edema with central macular thickness (CMT) >300um.

Exclusion criteria

1. Cases with proliferative diabetic retinopathy.
2. Cases with any macular disease other than diabetic maculopathy.
3. Cases with history of cataract surgery within 12 months.
4. Cases with significant cataract which interferes with OCT.

Base line evaluation

One week preoperative all patients had:

- Full history including medical history; duration of diabetes and other systemic diseases.
- HbA1C (glycosylated hemoglobin), kidney functions Serum lipids were assessed.
- Complete ophthalmological examination were conducted to all patient including best corrected visual acuity (BCVA) using snellen's chart anterior segment and fund us examination.
- Intraocular pressure measurement using Goldman applanation tonometry.
- Pre-interventional fluoresce in angiography using Topcon TRC 50DX retinal camera (Topcon Optical Co., Tokyo, Japan).
- Optical coherence tomography (OCT) to document macular thickness using spectral domain (SD) OCT (Optovue, Northport loop west Fremont, CA, USA).

Informed consent

The patients signed consent for intervention including: advantages, disadvantages, risks of possible complications.

Follow-up

Patients were followed up for six months for: BCVA using Snellen chart, change in central macular thickness using macular OCT and any detected complication (basic clinical evaluation was repeated at every visit). Follow up visits were held up at two weeks, one month post every injection and finally at six months.

Statistical Analysis

The collected data was organized, tabulated and statistically analyzed using SPSS software statistical computer package version 19 (SPSS Inc, USA). For quantitative data, the mean and standard deviation were calculated. Comparison between study subgroups was done using Mann-Whitney test. Freidman test was performed to compare between values of CMT and BCV at different times. Qualitative data were described as frequencies (number of cases) and percentages, chi- square test or Fischer exact test was used as a test of significance. For interpretation of results of tests of significance, significance was adopted at $P \leq 0.05$.

3. Results:

Between May 2015 and March 2017, twenty eyes of twenty patients which met the inclusion criteria were enrolled in the study. The patients received three monthly intra vitreal injection of 0.5mg/0.05ml ranibizumab were randomly divided into two groups. All patients completed the follow up period (six months).

Patient Characteristics

As shown in table (1), the mean age was **56.4 ± 7.1**years. Thirteen cases (65%) were Phakic and 7 cases (35%) were pseudophakic. The mean value of HbA1c was **7.7% ± 0.9.** The mean duration of DM was **10.9 ± 5.6** years. Eleven patients (55%) were hypertensive.

Table (1): Basal characteristics of the study population.

Variable	INJECTION (n=20)	P value
Age (years)	**56.4 ± 7.1**	**0.111**
Sex	Males: 10 Females: 10	0.525
HA1c	**7.7 ± 0.9**	**0.790**
Lens status	Phakic 13(65%) Pseudophakic 7(35%)	0.744
Fund us fluoresce in angiography	One case ischemic maculopathy 5%	
BCVA (log MAR)	**0.97 ± 0.19**	**0.275**
CMT	**474.30 ± 120.97**	**0.034***
Mean IOP	14.89 ± 2.98mm**Hg**	0.406
Cholesterol	201.95 ± 36.71	0.650

Central Macular Thickness (CMT)

The mean CMT changed from **474.30 ± 120.97**um (319-680) at base line to **389.55 ± 85.99**um (287-600) at 6 months. At three months, all cases showed reduction in CMT; one case (5%) showed reduction in CMT >50%, four cases (20%) showed reduction 30%-50%, five cases showed reduction 20 %-< 30% and ten cases showed reduction <20%.

At six months, seventeen cases showed reduction in CMT (85%). five cases (50%) showed reduction 30%-50% and four cases (20%) showed reduction 20 %-< 30 %, eight cases (40%) showed reduction <20 %.

Visual acuity

The mean BCVA (log MAR) changed from **0.97 ± 0.19** at base line to **0.79 ± 0.24** at 6 months.

Table (2): BCVA at different times during the follow up period.

Variable	Injection group (N=20)	P-value
BCVA preoperative	**0.97 ± 0.19**	**0.275**
BCVA 2 weeks	**0.85 ± 0.18**	**0.898**
BCVA 3 months	**0.74 ± 0.21**	**0.696**
BCVA 6 months	**0.79 ± 0.24**	**0.464**

The mean visual gain was 2.00 ± 2.00 lines. Thirteen patients (65%) showed improvement in BCVA; six patients (30%) showed improvement in BCVA >three lines, one patient (5%) showed improvement three lines, six patients showed reduction < three lines. Seven patients (35%) showed the same basal visual acuity, three of them had the same BCVA throughout the sixth months and four cases had decreased BCVA after three months. Two of the three cases that had the unchanged BCVA showed interrupted ellipsoid zone in OCT and the third case had ischemic maculopathy. There was no correlation between basal CMT and final visual gain.

Associated factors (predictors of response)

Type of treatment of DM, lipid profile and lens status was all insignificant on the results of vision gain or decrease in CMT (Table 3). There was no correlation between HA1c and duration of DM either with visual or anatomical improvement.

Table (3): Correlation of CMT and BCVA at 3 and 6 months with different study parameters.

	CMT 3m		**CMT 6m**		**BCVA 3m**		**BCVA 6m**	
	r	**P-value**	**r**	**P-value**	**r**	**P-value**	**R**	**P-value**
Age	0.121	0.612	0.102	0.667	-0.095	0.691	-0.094	0.693
Duration of DM	0.358	0.121	0.285	0.223	0.221	0.348	0.111	0.640
HA1c	0.117	0.623	0.150	0.528	0.420	0.065	0.241	0.306
Cholesterol	0.119	0.629	0.062	0.800	-0.379	0.110	0.219	0.368

Table (4): Differences in CMT and BCV at 3 & 6 months in relation to types of diabetes treatment.

CMT 3m	**Insulin**	**330.33 ± 53.49**
	Oral	**339.89 ± 59.20**
	Combined	**397.20 ± 60.31**
	P-value	**0.148**
CMT 6m	**Insulin**	**410.83 ± 101.53**
	Oral	**359.78 ± 62.36**
	Combined	**417.60 ± 102.74**
	P-value	**0.393**
BCVA 3m	**Insulin**	**0.75 ± 0.24**
	Oral	**0.66 ± 0.11**
	Combined	**0.86 ± 0.27**
	P-value	**0.216**
BCVA 6m	**Insulin**	**0.87 ± 0.33**
	Oral	**0.70 ± 0.12**
	Combined	**0.88 ± 0.28**
	P-value	**0.303**

4. Discussion

Diabetic macular edema (DME) is a common manifestation of diabetic retinopathy that causes loss of central vision **(Bhagat et al., 2009**).

Multiple biochemical, inflammatory, mechanical, and molecular signaling factors play a role in pathogenesis of DME. Hyperglycemia-mediated accumulation of advanced glycation end products (AGEs) promotes neuro-vascular injury observed in DR. Hypoxia-mediated production of vascular endothelial growth factor (VEGF) results in intracellular signaling with phosphorylation of tight junction proteins leading to increased retinal vascular permeability and breakdown of blood-retina barrier **(Kim et al 2005).**

Variety of therapies has been studied with the aim of improving vision in more patients as well as preventing deterioration of VA in most. These include laser treatment, surgical options, intravitreal corticosteroids, intravitreal vascular endothelial growth factor (VEGF) inhibitors and other various new pharmacotherapies that are currently being investigated**.**

Nowadays intravitreal injection of anti-vascular endothelial growth factor (VEGF) is considered the gold standard for center involving DME. Unfortunately, anti-VEGF treatment regimens require that patient receive frequent assessments and numerous intravitreal injections at considerable cost over the course of several years. Recent studies showed that diabetic macular edema persists in 25%–64%of injected eyes in spite of repeated injections **(DRCR.net 2012, DRCR.net 2015).**

In our study the regimen of ranibizumab injection was three monthly injections similar to RESOLVE and RESTORE studies, however further injections (retreatment) were allowed only after completion of the six months.

All cases showed significant reduction in mean CMT at three months and seventeen cases (85%) at six months.

At three and six months the decrease in mean CMT was statistically significant in relation to base line value **(474.30, 351.35, 389.55 um at zero, 3, and 6 months respectively**), however the increase in CMT from three to six months was statistically significant; the CMT decreased progressively till three months and then re-increased significantly at six months. This result may be explained by wash out of anti VEGF from the vitreous after the stoppage of injection.

The BCVA changed from **0.97 Log MAR at base line to 0.74**,**0.79 Log MAR** at three and six months respectively and the mean gain was 2.00 ± 2.00 lines. The improvement in BCVA from base line to three and six months was significant, however the decrease in BCVA at six month was significant to three months value. At three months Seventeen cases showed improvement in BCVA (85%), while at six months thirteen cases (65%) showed improvement in BCVA. So in this group the improvement in BCVA was mainly at three months then started to decrease again at six months. This may be explained again by stoppage of injection after three months.

Three cases had zero response in visual gain throughout the follow up period in spite of decreased thickness. Two of them had interrupted ellipsoid zone and the third had ischemic maculopathy. Similar results were concluded with **Ashraf et al in 2016** and **Maheshwary et al 2010.**

Our results are matching with many previous studies on the efficacy of Ranibizumab in treating DME. The main conclusion of those studies was that ranibizumab is effective in management of DME on the anatomical and functional level; however multiple injections are required to obtain this result. The difference in our study was that we used three injections only over a six months period and this may explain the drop of vision and increase in CMT after three months.

Chun and associates in 2006 reported results of 10 patients treated with ranibizumab, 5 received 0.3 mg ranibizumab and 5 received 0.5 mg ranibizumab at baseline and at 1 and 2 months. At month 3, 40% of patients gained more than 15 letters, 50% gained more than 10 letters, and 80% obtained an improvement of at least 1 letter in BCVA. At month 3, the mean decrease in CMT was 45.3 and 197.8 μm in the low- and high-dose groups, respectively.

In READ-1 study, ten patients with DME received 0.5 mg IVR at baseline and at 1, 2, 4, and 6 months. Mean and median values of BCVA improved at 7 months by 12.3 and 11 letters respectively. Compared to the baseline, mean foveal thickness showed a significant 85% reduction; decreasing from 503 to 257 μm **(Nguyen et al., 2006).** This results are superior to ours and this may be related to different number of injections

In RESOLVE study 151 patients were randomized 1:1:1 to ranibizumab monotherapy at a dose of 0.3 or 0.5 mg or sham treatment. Patients received an initial treatment of three consecutive monthly injections and were followed monthly with an as-necessary regimen from month 3 to 12. At month 12, a mean increase in best corrected visual acuity (BCVA) of 11.8 letters in the 0.3 mg group and of 8.8 letters in the 0.5 mg group was noted, as compared with a reduction in BCVA of-1.4 letters in the sham group. Similar results were observed in central retinal thickness improvement, -194.2 versus -48.4 in the ranibizumab and sham groups, respectively (P value <0.001) **(Massin et al., 2010).**

In the RESTORE study, ranibizumab monotherapy or combined with laser versus laser monotherapy for DME, 345 patients were randomized 1:1:1 to 0.5 mg ranibizumab plus sham laser, 0.5 mg ranibizumab plus active laser, or sham injections with active laser. At months 12, mean change in BCVA was +6.1 letters in the ranibizumab monotherapy group, +5.9 letters in the group receiving combination therapy with ranibizumab and laser, and +0.8 letters in the laser alone group **(Mitchell et al., 2011).**

Similar results of the efficacy and safety of ranibizumab in DME were obtained with RISE, RIDE, DRCR Protocol T and I. In all these studies multiple injections were required to obtain and maintain the response of DME to IVR.

In their work on prediction of response of DME to TTT, **Ashraf et al in** 2016 found that, younger age, short duration of DM were associated with good visual and anatomical response, however in our study age and treatment of DM were not significantly related to response either anatomical or visual. This may be related to the relatively small number of patients in both groups.

There was no correlation between HA1c and duration of DM either with visual or anatomical improvement. This result is matching with **Macy et al** who found no correlation between HbA1c level and response to intravitreal treatment, however **Warid Al-Laftah et al** demonstrated that a greater proportion of patients with HbA1c<7% gained 2 lines of VA compared with those with HbA1c>7%, suggesting that poorer glycemic control may lead to worse visual outcome.

Transient IOP elevation was showed in three cases that were controlled by short course of anti-glaucoma and the development was the only encountered complications.

Intraocular pressure elevation with anti VEGF was reported in previous studies as **(Wu et al., 2008, Nicholson and Schachat, 2010).**

In conclusion, Intra vitreal ranibizumab injection is effective in treating DME. Outer retinal structure and ischemia in FFA were predictive in response to treatment.

Limitations

Our study is limited with small number of patients, short follow up period, more studies with larger sample size and longer duration of follow up are required to study in details factors affecting outcome of intra vitreal ranibizumab injection in management of DME.

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