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Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema

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ABSTRACT

Background: Diabetic macular oedema can occur at any stage of retinopathy and is typically characterized by retinal thickening and leakage of extracellular fluid, which are linked with hypoxia and up regulation of vascular endothelial growth factor (VEGF).

Objective: The aim of this study was to compare central macular thickness using optical coherence tomography (OCT) between Ranibizumab 0.5 mg monotherapy vs Ranibizumab 0.5 mg combined with laser based on mean average change in best-corrected visual acuity (BCVA) over 6 months in diabetic macular edema (DME).

Patients and methods: The study was carried out on forty eyes of patients aged 30-75 years old, with type 1 or 2 diabetes mellitus and have visual impairment due to DME. The patients were selected from the Outpatient Ophthalmology Clinic of Aswan University Hospital. **Results:** Visual acuity measured as log MAR values in Group A, when comparing the baseline visual acuity with that at the end of follow-up period, there was a significant improvement in vision. Some patients achieved improvement of two lines at the end of six months. In Group B, there was a significant improvement in vision when comparing the baseline reading with the six months reading with an average gain in visual acuity of two or more lines. The central macular thickness improved in both groups without statistically significant difference between them in the first three months post-injection. However, the combined group achieved the highest reduction in the macular thickness at the end of follow-up period. **Conclusion:** Ranibizumab monotherapy provided significantly superior benefit over standard-of-care laser in patients with visual impairment due to DME being rapidly improved and sustained BCVA over the 6-month treatment period.

Keywords: Ranibizumab Monotherapy, Diabetic Macular Edema, BCVA, OCT.

INTRODUCTION

Diabetic macular edema (DME) has an estimated prevalence ranging from 0-3% in persons diagnosed as diabetics for the first time. This incidence increases to 30% after 10 years of onset of diabetes [(1)].

Diabetic Retinopathy results in retinal ischemia (i.e., microaneurysms, hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, or macular edema) and/or signs of increased retinal vascular permeability. Loss of vision is a consequence of various pathophysiological mechanisms including neovascularization that may cause vitreous hemorrhage, retinal detachment, or capillary nonperfusion [(2)]. Retinopathy occurs in most patients with DM of longer duration, though its incidence can be reduced by aggressive control of hyperglycemia and hypertension [(3)].

Laser photocoagulation, a traditional standard treatment for DME, has been widely used for several decades in spite of some limits [(3)]. Laser photocoagulation prevents degradation of vision by reducing leaky microaneurysms and inhibiting extravasation of fluid into the macula, which is the purpose of laser photocoagulation [(4)].

Until the introduction of anti-VEGF agents, which are known to reduce total retinal thickness, IVR also become an effective. Ranibizumab, one of the anti-VEGF agents, is the first antigen-binding humanized monoclonal antibody segment that has the FDA approval for therapeutic strategy for DME. It has been reported that the significant reduction of the plasma levels of VEGF in patients with DME were found after the intravitreal injection of ranibizumab [(3)].

AIM OF THE STUDY

The aim of this study was to compare central macular thickness using optical coherence tomography (OCT) between ranibizumab 0.5 mg monotherapy over ranibizumab 0.5 mg combined with laser based on mean average change in best-corrected visual acuity (BCVA) over 6 months in diabetic macular edema (DME).

PATIENTS AND METHODS

Study design: Randomized prospective interventional study.

Patient selection:

The study was carried out on forty eyes of patients aged 30-75 years old, with type 1 or 2 diabetes mellitus and have visual impairment due to DME. The patients were selected from the Outpatient Ophthalmology Clinic of Aswan University Hospital.

Inclusion criteria:

1. Stable medication for the management of diabetes within 3 months before study.
2. Visual impairment due to focal or diffuse DME.
3. BCVA 6/9-6/60 based on (ETDRS).
4. Decreased vision due to DME and not for other causes.

Exclusion criteria:

1. Presence of significant ocular disorders affecting vision e.g. Cataract, glaucoma and uveitis.

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2. Laser photocoagulation in the study eye for the last 3 months.
3. Presence of macular ischemia.
4. Any history of any intraocular surgery in the study eye within the past 3 months.
5. Patients with uncontrolled systemic diseases.
6. History of stroke.

Ethical consideration and Written informed consent :

An approval of the study was obtained from Aswan University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the operation.

Methods:

Forty eyes were assigned to one of the following 2 groups according to the regimen used in the management of diabetic macular edema. Each group consists of 20 eyes:

- **Group A:** 20 eyes who randomized to be injected with 0.5 mg ranibizumab (0.1ml) at baseline, 1st month and 3rd month
- **Group B:** 20 eyes who randomized to be injected with 0.5 mg ranibizumab at baseline, 1st month, and 3rd month followed with macular grid argon laser photocoagulation three weeks after the 1st injection.

❖ **History taking:**

Age.

Duration of diabetes, any systemic disease and drug intake.

Type, duration, and onset of diminution of vision.

Previous ocular surgery or interventions.

❖ **Assessment of uncorrected and best corrected visual acuity:**

All visual acuity results were transformed to the common logarithm of the minimum angle of resolution (Log MAR).

❖ **Slit-lamp examination:**

To assess anterior segment for any abnormalities (cataract, corneal opacities).

❖ **FFA:** A colored photo of the fundus was taken at first prior to injection.

❖ **Macular OCT:** Macular OCT was done to detect the presence of retinal thickening, cystoid macular edema, hard exudates and vitreoretinal interface.

Baseline central retinal characteristics were analyzed by OCT through a dilated pupil.

Retinal thickness was defined as the distance between the inner retinal surface (defined as the interface between the dark vitreous and the bright reflection of ILM) and the outer retinal surface that is defined as the inner surface of bright RPE/Bruch's membrane interface. Also, scans were graded for the presence of specific morphological patterns of macular edema.

Follow up:

Visual acuity as log MAR value, central macular thickness (CMT) measured with optical coherence tomography (OCT), were assessed at baseline, 1, 3 and 6 months post-injection.

Post-operative:

The patients were monitored for potential injection related complications by measurement of BCVA, anterior segment and posterior segment evaluation at 1, 3 and 7 days after injection.

The anatomical and functional responses to treatment were followed up at 1, 3 & 6 months after baseline injection.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Paired sample t-test of significance was used when comparing between related samples.
- Chi-square (x^2) test of significance was used in order to compare proportions between qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:

▪ Probability (P-value)

– P-value <0.05 was considered significant.
– P-value <0.001 was considered as highly significant.
– P-value >0.05 was considered insignificant.

RESULTS

The demographic data of the patients included in the study groups are shown in table (2). The study was carried out on forty eyes of patients aged 30-75 years old, with type 1 or 2 diabetes mellitus and have visual impairment due to DME. There were 20% male and 80% female patients in the group A (IR group), while in the group B (combined group), there were 35% male and 65% female patients.

Table (1): A Comparison between groups according to demographic data.

	Demographic data	Group A *(n=20)*	Group B *(n=20)*	t/x2#	p-value
Age (years)	Mean ± SD Range	55.75 ± 4.66 47-68	58.35 ± 5.14 45-65	2.81	0.102
Sex	Female Male	16 (80.0%) 4 (20.0%)	13 (65.0%) 7 (35.0%)	1.129#	0.288

*t-Independent Sample t-test; #x^2: Chi-square test, p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS*

This table showed no statistically significant difference between groups according to demographic data.

Table (2): A Comparison between groups according to other systemic disorder.

Other systemic disorder	Group A *(n=20)*	Group B *(n=20)*	x2	p-value
HTN	4 (20.0%)	7 (35.0%)	1.129	0.288
No	16 (80.0%)	13 (65.0%)		

x^2: Chi-square test; p-value >0.05 NS

This table showed no statistically significant difference between groups according to other systemic disorder.

Table (3): A Comparison between groups according to which eye affected.

Which eye affected	Group A *(n=20)*	Group B *(n=20)*	x2	p-value
Left	7 (35.0%)	10 (50.0%)	0.92	0.337
Right	13 (65.0%)	10 (50.0%)		

x^2: Chi-square test; p-value >0.05 NS

This table showed no statistically significant difference between groups according to which eye was affected.

Table (4): A Comparison between groups according to duration of diabetes (years).

Duration of diabetes (years)	Group A *(n=20)*	Group B *(n=20)*	t-test	p-value
Mean ± SD	15.25 ± 3.63	13.00 ± 2.43	1.318	0.267
Range	11-25	7-16		

t-Independent Sample t-test; p-value >0.05 NS

This table showed no statistically significant difference between groups according to duration of diabetes (years).

Changes in visual acuity over the follow up period:

Visual acuity measured as log MAR values in **group A**, when comparing the baseline visual acuity with that at the end of follow-up period, there was a significant improvement in vision and some patients achieved improvement of two lines at the end of six months. In **group B,** there was a significant improvement in vision when comparing the baseline reading with the six months reading with an average gain in visual acuity of two or more lines. Vision gain was achieved in both groups throughout the follow-up period with no significant difference between them but the effect was more pronounced and long lasting in the combined group (group B) than the IR group (group A) as shown in table (5).

Table (5): A Comparison between groups according to BCVA.

	BCVA	Group A *(n=20)*	Group B *(n=20)*	t-test	p-value
Before	Mean ± SD Range	0.81 ± 0.08 0.6-0.9	0.78 ± 0.08 0.6-0.9	0.908	0.347
1st month after injection	Mean ± SD Range	0.64 ± 0.10 0.5-0.8	0.67 ± 0.09 0.5-0.8	0.712	0.404
3rd month after injection	Mean ± SD Range	0.58 ± 0.07 0.5-0.7	0.62 ± 0.08 0.5-0.8	1.353	0.493
6th month after injection	Mean ± SD Range	0.53 ± 0.05 0.5-0.6	0.57 ± 0.07 0.4-0.7	0.651	0.36

t-Independent Sample t-test; p-value >0.05 NS

This table showed no statistically significant difference between groups according to BCVA.

Table (6): A Comparison between before with other category according to BCVA in each group.

BCVA	Group A *(n=20)*			Group B *(n=20)*		
	Mean ± SD	Mean Diff.	p-value	Mean ± SD	Mean Diff.	p-value
Before	0.81 ± 0.08			0.78 ± 0.08		
1st month after injection	0.64 ± 0.10	0.17	<0.001**	0.67 ± 0.09	0.12	<0.001**
3rd month after injection	0.58 ± 0.07	0.23	<0.001**	0.62 ± 0.08	0.16	<0.001**
6th month after injection	0.53 ± 0.05	0.28	<0.001**	0.57 ± 0.07	0.22	<0.001**

*t-Paired Sample t-test, *p-value <0.05 S; **p-value <0.001 HS*

This table showed statistically significant difference between before with other category according to BCVA in each group.

Central macular thickness (CMT) changes:

The central macular thickness improved in both groups without statistically significant difference between them in the first three months post-injection, however the combined group achieved the highest reduction in the macular thickness at the end of follow-up period. This difference was not statistically significant (Table 7).

Table (7): A Comparison between groups according to CMT.

CMT	Group A *(n=20)*	Group B *(n=20)*	t-test	p-value
Before Mean ± SD Range	420.00 ± 89.05 297-606	422.40 ± 29.20 377-490	0.013	0.909
1st month after injection Mean ± SD Range	357.20 ± 87.22 218-518	355.10 ± 44.51 212-402	0.009	0.924
3rd month after injection Mean ± SD Range	281.35 ± 83.04 187-450	241.45 ± 36.32 166-310	2.091	0.156
6th month after injection Mean ± SD Range	260.60 ± 66.78 188-405	229.45 ± 34.51 158-295	3.434	0.072

t-Independent Sample t-test; p-value >0.05 NS

This table shows no statistically significant difference between groups according to CMT.

Table (8): A Comparison between before with other category according to CMT in each group.

CMT	Group A *(n=20)*			Group B *(n=20)*		
	Mean ± SD	Mean Diff.	p-value	Mean±SD	Mean Diff.	p-value
Before	420.00 ± 89.05			422.40 ± 29.20		
1st month after injection	357.20 ± 87.22	62.800	0.011*	355.10 ± 44.51	67.30	0.007*
3rd month after injection	281.35 ± 83.04	138.650	<0.001**	241.45 ± 36.32	180.95	<0.001**
6th month after injection	260.60 ± 66.78	159.400	<0.001**	229.45 ± 34.51	192.95	<0.001**

*t-Paired Sample t-test, *p-value <0.05 S; **p-value <0.001 HS*

This table showed statistically significant difference between before with other category according to CMT in each group.

DISCUSSION

This study showed that treatment with anti-VEGF in addition to grid laser is effective and safe in the management of DME during a period of 6 months. However, our findings revealed that functional results in the **IR + Grid** laser group were slightly higher (though not statistically significant) compared to the **IR** treatment group in an earlier treatment phase. This suggests that focal laser therapy in the eyes with DME is justified.

Our study also demonstrated that the CMT was decreased throughout the time of the study both in the combination therapy and the ranibizumab groups, but the combination therapy group achieved a greater reduction of the CMT that persisted until the end of the follow-up time. As an explanation for greater improvement of the visual acuity and CMT in the combination therapy group than the monotherapy group in this study is that diffuse DME is caused by a widespread microvascular leakage that is considered an advanced and chronic stage of DR. So, adding supplemental treatment to the anti-VEGF therapy would potentiate its therapeutic effect.

Macular laser photocoagulation seems to be responsible for the improved functional and anatomical results in the combination therapy group. Laser destroys some of photoreceptors, which consume a high amount of oxygen. This will preserve and increase the oxygen supply to the inner retinal layers. Consequently, this would decrease the retinal anoxia and reduce further releases of VEGF and subsequently improving the results and reducing the recurrence rate of DME. Hence, the use of macular laser photocoagulation with intravitreal ranibizumab injection is practically more appropriate in regaining

good visual and anatomical results than ranibizumab or laser alone.

Wang *et al.* [5], in a meta-analysis study was trying to demonstrate the efficacy of intravitreal ranibizumab injection for treatment of DME. They concluded that ranibizumab alone or combined with laser were more advantageous than laser monotherapy.

Current treatment options for DME allowed for varied and increasingly complex combinations of treatment paradigms like laser monotherapy, combination of laser therapy with anti-VEGF agents (RBZ, bevacizumab, aflibercept), anti-VEGF monotherapy and sustained-release corticosteroid therapy (dexamethasone, either as a monotherapy or in combination with the other therapies). Other studies, however, showed that visual acuity deteriorated by about three lines or more in about quarter of eyes with diffuse DME after macular laser photocoagulation **[6].**

READ-2 is a multicenter clinical study established to compare ranibizumab with macular laser, alone or in combination, for the treatment of DME. The study found that the ranibizumab group achieved a significant gain in visual acuity compared to patients who had only laser treatment after six months of the study. It was also found that the combination therapy group didn't have statistically significant different results than the monotherapy groups (laser alone or ranibizumab alone) as regard the visual acuity changes. As regard the anatomical results, the study revealed that ranibizumab alone or combined with laser resulted in greater reduction of the CMT than laser monotherapy **[7].**

Results from the RESTORE study demonstrated that ranibizumab alone or combined with laser were superior to laser monotherapy in improving visual acuity and reducing the CMT throughout the12 months. In addition, it revealed that at one year, no differences were found between the ranibizumab alone or combined with laser regarding the anatomical and functional results **[8]**. The results of RESTORE study are in line and consistent with the Diabetic Retinopathy Clinical Research Network (DRCR.net) and RESOLVE trials.

The DRCR.net trial revealed that intravitreal ranibizumab injection adjunctive with macular laser treatment either prompt or deferred was significantly more efficient than laser monotherapy in restoring good visual and anatomical results in DME patients after 12 months of therapy. This trial suggested that combined treatment could provide a more potent regimen for treatment of DME, taking into consideration the multifactorial etiology of the disease **[9].** The RESOLVE trial also showed that ranibizumab yielded a fast and long-lasting improvement in visual acuity results when compared to sham in a time of one year follow-up **[10]**.

Some previous trials used laser therapy within one week after the first intravitreal ranibizumab injection. The accumulation of much fluid in the retinal tissues in patients suffering from diffuse macular edema may make thermal therapy more difficult, less efficient and requiring the delivery of more laser energy than usual that could result in more visual deterioration **[11]**. That is why in our study, we applied laser treatment three weeks after the first ranibizumab injection allowing the retina to get rid of some retinal fluid facilitating and making the laser application more easy and efficient.

It remains to be shown whether, if the eyes with extensive exudative material in the central macular region and reduced BCVA would profit from an individualized and more intense anti-VEGF treatment strategy, as has been suggested by others previously **[12].** Our results are in agreement and in line with the previously mentioned studies concerning the anatomical and functional results.

Whereas laser therapy still the standard treatment of DME, the appearance of anti-VEGF agents have opened up a new era in the treatment of DME that could enhance, limit, or even replace thermal therapy **[13]**.

In conclusion the use of more than one line of treatment for patients with diffuse DME could provide more sustained results with the need for less frequent injections and decreasing the recurrence or persistence rate of DME. Further studies with large number of patients and longer follow-up periods are needed to evaluate the safety and efficacy of combination therapy for DME over a longer time span.

CONCLUSION

Ranibizumab monotherapy provides significantly superior benefit over standard-of-care laser in patients with visual impairment due to DME, rapidly improving and sustaining BCVA over the 6-months treatment period. Ranibizumab therapy was administered using an individualized PRN regimen with monthly monitoring and retreatment based on disease stability. During the 6-month study period combining laser with ranibizumab did not seem to provide any advantage compared to ranibizumab monotherapy in terms of improving BCVA and treatment exposure. However, longer follow-up may be required to assess the benefit of combining laser with ranibizumab. Ranibizumab consistently improved BCVA across all the subgroups of patients, including patients with focal or diffuse DME.

Ranibizumab was well-tolerated in patients with visual impairment due to DME with a safety profile similar to the well-established safety profile in neovascular AMD.

REFERENCES

1. **Klein R, Knudtson MD, Lee KE *et al.* (2009):** The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty five- year incidence of macular edema in

persons with type 1 diabetes. Ophthalmology, 116: 497–503.

2. **Zehetner C, Kirchmair R, Huber S *et al.* (2017):** Burdon, Diabetic macular oedema: clinical risk factors and emerging genetic influences. Clinical and Experimental Optometry, 100 (6): 569–576.
3. **Kusuhara S, Fukushima Y, Ogura S *et al.* (2018):** Pathophysiology of Diabetic Retinopathy: The Old and the New. Diabetes Metab J., 42 (5): 364–376.
4. **Qian TW, Zhao MY, Li XX *et al.* (2017):** Efficiency and safety of laser photocoagulation with or without intravitreal ranibizumab for treatment of diabetic macular edema: a systematic review and Meta-analysis. Int J Ophthalmol., 10(7): 1134–1143.
4. **Au A, Singh RP (2016):** A multimodal approach to diabetic macular edema. J Diabetes Complicat., 30 (3): 545-553**.**
5. **Wang H, Sun X, Liu K *et al.* (2012):** Intravitreal ranibizumab (Lucentis) for the treatment of diabetic macular edema: a systematic review and meta-analysis of randomized clinical control trials. Cur Eye Res., 37: 661–70.
6. **Lee CM, Olk RJ (1991):** Modified grid laser photocoagulation for diffuse diabetic macular edema: long term visual results. Ophthalmology, 98: 1594–602.
7. **Nguyen QD, Shah SM, Khwaja AA *et al.* (2010):** READ-2 Study Group. Two-year outcomes of the Ranibizumab for Edema of the mAcula in Diabetes (READ-2) Study. Ophthalmology, 117: 2146 –51.
8. **Mitchell P, Bandello F, Schmidt-Erfurth U *et al.* (2011):** The RESTORE study: Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology, 118: 615–25.
9. **Elman MJ, Bressler NM, Qin H *et al.* (2011):** Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology, 118:609–14.
10. **Massin P, Bandello F, Garweg J *et al.* (2010):** Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE study): a 12-month, randomized, controlled, doublemasked, multicenter phase II study. Diabetes Care, 33: 2399 – 405.
11. **Comyn O, Sivaprasad S, Peto T *et al.* (2014):** A randomized trial to assess functional and structural effects of ranibizumab versus laser in diabetic macular edema (the LUCIDATE study). Am J Ophthalmol., 157: 960 – 970.
12. **Mehta H, Fraser-Bell S, Yeung A *et al.* (2016):** Efficacy of dexamethasone versus bevacizumab on regression of hard exudates in diabetic maculopathy: data from the BEVORDEX randomised clinical trial. British Journal of Ophthalmology, 10 (7): 1000–1004.
13. **Ford JA, Lois N, Royle P *et al.* (2013):** Current treatments in diabetic macular oedema: systematic review and meta-analysis. BMJ Open, 3 (3): 2269-73.