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**RANIBIZUMAB MONOTHERAPY VERSUS COMBINED  
RANIBIZUMAB PLUS TRIAMCINOLONE FOR  
TREATING DIABETIC MACULAR EDEMA;  
EVALUATION AFTER SINGLE INJECTION****Fareed A AL-Laftah**

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**Abstract**

Anti vascular endothelial growth factor (Anti-VEGF) have been proved to be the main treatment for DME and also steroids showed a significant role in resolution of diabetic macular edema(DME). Based on concept of multifactorial causes of DME, this study proposed theoretically an adjuvant effects for steroids in combination with anti-VEGF for DME, the multifactorial complex pathogenetic mechanisms require a comprehensive approach.

This study compares the outcome of monotherapy of intravitreal Ranibizumab injection in one eye versus combined therapy of Ranibizumab+Triamcinolone in other eye of the same patient.

This study includes prospective consecutive interventional case series study. Patients with bilateral diabetic macular edema given Lucentis dose was 0.05 ml = 0.5 mg in on eye and Triamcinolone 0.05 ml = 2 mg in the other eye.

Thirty patients with bilateral diabetic macular edema were enrolled in this study, all have perfused macula. The mean age at the start of the study was 54 years.

The study has shown a promising results for the treating diabetic macular edema with combined therapy of Ranibizumab and Triamcinolone

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**Introduction**

**D**iabetes mellitus (DM) is a major cause of avoidable blindness in both the developing and the developed countries. Patients with diabetic retinopathy (DR) are 25 times more likely to become blind than non-diabetics<sup>1</sup>. Macular edema is a major cause of central vision impairment in patients with diabetic retinopathy<sup>2</sup>.

The pathogenesis of diabetic macular edema (DME) is multifactorial. Breakdown of the blood-retina barrier (BRB) increases retinal capillary permeability leading to retinal edema<sup>3,4</sup>. It has been reported that one of the histologic changes associated with the development of diabetic macular edema is loss of pericytes, the loss of pericytes may be related to accumulation of Advanced Glycation End Products and to the presence of inflammatory mediators and is

associated with the formation of microaneurysms and the breakdown of the BRB<sup>5,6</sup>.

Pathogenesis of Diabetic macular edema also includes activation of vascular endothelial growth factors which causes an increase in vascular permeability<sup>7</sup>. VEGF plays a major role in breakdown of the blood-retina barrier<sup>8</sup>. Inflammation is an eminent factor in diabetic macular edema, in particular via leukostasis within retinal capillaries. The anti-inflammatory activity of corticosteroids is related to several paths of action, including inhibition the phospholipase A2 pathway, and reduce leucocyte chemotaxis<sup>8</sup>. Corticosteroids also inhibit the expression of VEGF and VEGF gene<sup>9</sup>.

Anti-VEFG has been proved to be the main treatment for DME and also Steroids showed a significant role in resolution of

DME. Based on concept of multifactorial causes of DME, currently there are many combined treatment for DME such as Intravitreal Triamcinolone plus Macular Laser Photocoagulation, evaluated the clinical outcome of macular laser photocoagulation after intravitreal triamcinolone acetonide (IVTA) for diffuse DME<sup>10</sup>. Intravitreal Ranibizumab plus Macular Laser Photocoagulation (READ2), compared the efficacy of intravitreal ranibizumab with focal/grid laser and a combination of both in 126 patients with DME<sup>11</sup>.

We are proposed theoretically an adjuvant effects for Steroids in combination with anti-VEGF for DME, the multifactorial complex pathogenetic mechanisms require a comprehensive approach. In this study we are comparing the outcome of monotherapy (Intravitreal Ranibizumab injection in one eye) versus combined therapy (Ranibizumab+ Triamcinolone in other eye of the same patient).

### Patients & Methods

This is a Prospective consecutive interventional case series study, Which included patients who were attending retina clinic with bilaterally center involved diabetic macular edema either being or not being treated before, and we excluded those who was having treatment for DME in the last 6 months (Intravitreal Injection, Laser, Vitrectomy), patients with glaucoma or significant cataract, retinal co-pathology as vein occlusion or significant hypertensive retinopathy.

Consent has been taken and explained to patient about risk/benefits of being injected with two medicines and side effects of steroids.

Assessment: all patients underwent a thorough ophthalmic examination including; Visual Acuity (VA) assessment and recoded as LOGMAR to simplify the statistical analysis, Intraocular Pressure (IOP) measured by applanation tonometry, Lens status, Grading of

Diabetic Retinopathy. DME was assessed and categorized by Optical Coherence Tomography (OCT) in the initial visit (Pre-injection visit) measuring Total Macular Volume (TMC), Central Foveal Thickness (CFT), and classifying types of DME into 3 main types: Diffuse, Mixed and Cystoid Macular Edema. Fundus Fluorescein Angiography (FFA) was done to assess the perfusion status of macula and those with significant Macular ischemia have been excluded from study group.

All intravitreal injection done in the theatre room to ensure sterilization environment and performed under topical anesthesia, pre-injection conjunctival betadine 5% drops used for sterilization and the injection done 3.5-4 mm temporally to limbus. Lucentis dose was 0.05 ml = 0.5 mg and TA was 0.05 ml = 2 mg, no paracentesis done or immediate anti-glaucoma drug is given in all cases, prophylactic antibiotics eye drops applied 3 times for 3 days post-injection, VA check, IOP, Lens examination, and OCT were repeated on follow up visits (6 weeks and 12 weeks).

Statistical analysis done by using SPSS software (Independent-Samples T-test) to compare the means of different factors on 3 occasions (baseline, after 6, and 12 weeks)

### Results

Thirty five patients were initially included, five of them have been removed from statistical study because of no regular checkup was done in the proposed time intervals.

Standardization of the patient parameters and cofactors was eliminated in this study as we compared eyes of the same patient. Thirty patients with bilateral diabetic macular edema were enrolled in this study, all have perfused macula. The mean age at the start of the study was 54 years. Additional patient demographics and baseline characteristics are listed in table I.

**Table I: Baseline Characteristics of the Study Population**

<b>Age:</b>		
Age Mean $\pm$ SD	54 $\pm$ 9 years	
<b>Sex:</b>		
Female	19	
Male	11	
<b>DR Grade:</b>	<b>(Lucentis Group)</b>	<b>(Combined Group)</b>
NON-PDR	1	1
Pre-PDR	2	3
PDR	4	3
Stable PDR + PRP	9	9
P-Value = 0.924 for DR between 2 groups (Independent sample test)		
PDR= Proliferative Diabetic Retinopathy		
<b>Oct Type:</b>		
DIFFUSE	6	2
MIXED	19	19
CME	5	9
P-Value = 0.876 for OCT type between 2 groups (Independent sample test)		

All patients received single Intra-Vitreous injection of ranibizumab monotherapy 0.5 mg in one eye and combined therapy of ranibizumab 0.5 mg +Triamcinolone 2mg in the other eye, and assessed on 3 occasions; baseline before injection, 6 weeks and 12 weeks after injection (Table II), assessment was mainly for changes in Visual Acuity recorded as LOGMAR, intraocular pressure in mmHg, Total Macular Volume (TMV) in mm<sup>3</sup>, central foveal thickness (CFT) in  $\mu$ m, Tables (III) and (IV). Statistical analysis done by SPSS Version 21, General Linear Model, Repeated Measures Analysis.

Initial assessment were to check for grading of Diabetic Retinopathy, and categorizing DME by OCT, Table (I). There was no significant differences between the two groups for severity of diabetic retinopathy and OCT type of DME, P-Value was 0.924, 0.876 respectively. Statistical analysis done by SPSS Version 21, Independent sample test

#### **Visual Acuity (VA):**

Overall, both Ranibizumab monotherapy and combined Therapy (Ranibizumab + Triamcinolone) resulted in improvement of VA by 2 lines in Snellen VA chart in the first 6 weeks after injection, however

VA was stabilized in monotherapy group till 12 weeks of follow-up, and improved by one more line in Snellen VA chart in combined therapy group. Figure 1, statistically the VA progression over 3 months after injection was not comparable between 2 groups, P-Value was statistically not significant in monotherapy group (0.98) Table (II), and P-Value was statistically significant in combined group (0.02) Table (III).

#### **Intraocular Pressure (IOP):**

IOP level in all patient was stable over 3 months in monotherapy group, while in combined group, IOP showed spike at 6 weeks after injection and declined to the baseline level at 12 weeks interval after combined injection Figure 2, Tables (II), (III).

#### **Total Macular Volume (TMV)**

At 6 weeks after intravitreal injection, the volume of diabetic macular edema was significantly minimized in both groups, 11.8 mm<sup>3</sup> to 10.9 mm<sup>3</sup> in Ranibizumab group and 12.4 mm<sup>3</sup> to 10.7 mm<sup>3</sup> combined group, however, at 12 weeks the effect of Ranibizumab was stabilized and the macular volume remained unchanged, from 10.88 to 10.87 mm<sup>3</sup>, but

the late effects of combination of Ranibizumab and Triamcinolone was amplified and TMV significantly decreased more from 10.7 to 10.4 mm<sup>3</sup>, Tables (II), (III), Figure 3.

**Central Foveal Thickness (CFT)**

The outcome of monotherapy and

combined intravitreal injection was comparable on the CFT; in the initial 6 weeks was from 352 to 307 micron in Ranibizumab group and from 418 to 312 micron in combined group and then stabilized in both group till 12 weeks after injection, Tables (II), (III), Figure 4.

**Table II: Various parameters at 3 time points among monotherapy group (M±SD)**

Variable	Baseline	6 weeks	12 weeks	P-VALUE
VA(LOGMAR)	0.4587±0.35189	0.3420±0.27918	0.3413±0.280	0.98
IOP	15.13±1.655	15.43±1.547	15.53±1.676	0.585
TMV	11.797±1.8854	10.887±1.3533	10.870±1.3311	0.03
CFT	352.13±126.237	307.13±80.957	313.47±78.986	0.01

**Table III: Various parameters at 3 time points among combined therapy group (Mean ± SD)**

Variable	Baseline	6 weeks	12 weeks	P-value
VA (LOGMAR)	0.5333±0.30635	0.3993±0.22981	0.2947±1.890	0.02
IOP	15.20±1.518	19.30±6.390	15.97±1.903	0
TMV	12.367±1.7519	10.70±1.3057	10.373±1.3575	0
CFT	418.03±132.541	311.67±92.147	307.77±90.574	0

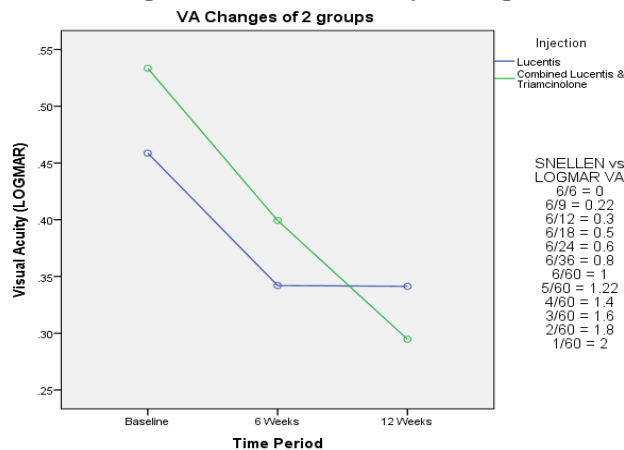
**Lens Status**

There was no changes in lens status except for 2 patients developed cataract at 12 weeks after combined Ranibizumab and Triamcinolone Injection, Table (IV).

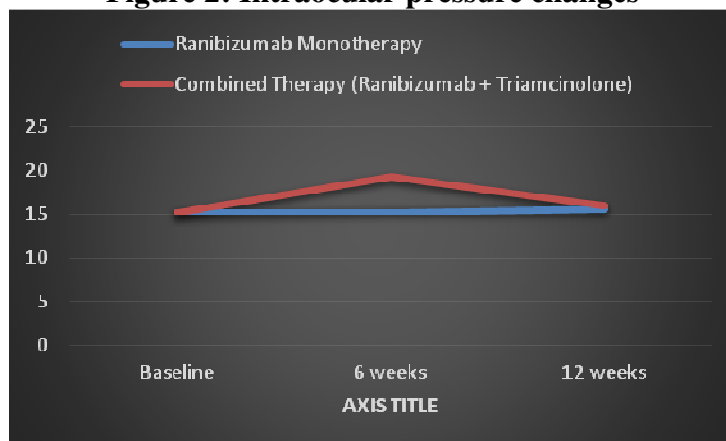
**Table IV: Cataract changes in 2 groups**

Injection Group	Cataract		
	Baseline	6 weeks	12 weeks
Ranibizumab Monotherapy	2	2	2
Combined Therapy	0	0	2

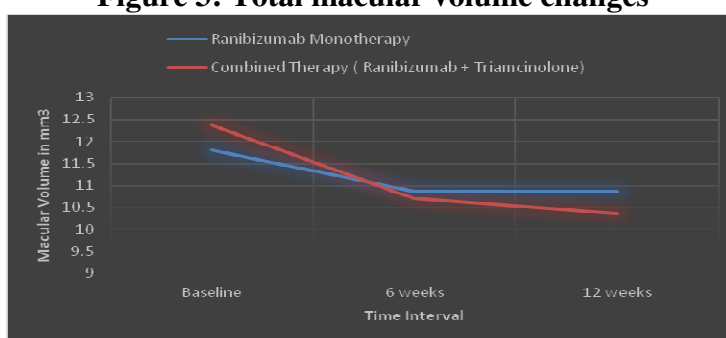
**Figure 1: Visual acuity changes**



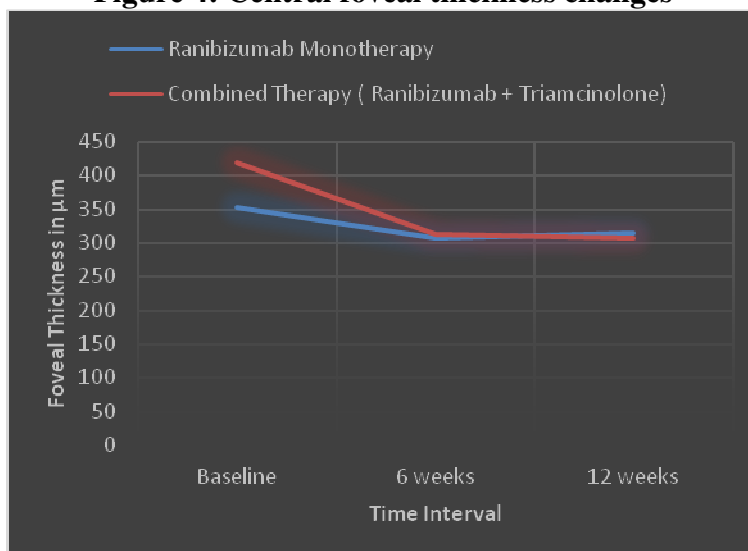
**Figure 2: Intraocular pressure changes**



**Figure 3: Total macular volume changes**



**Figure 4: Central foveal thickness changes**



**Discussion**

Old studies of the ETDRS, have proved that macular laser photocoagulation was the main step for treating DME, however, results have not been adequate for visual acuity<sup>2</sup>. The founding of intravitreal corticosteroids and anti- VEGF treatments altered the therapeutic strategy of DME.

The Combination therapy of Intravitreal injecting with laser treatment is found to be superior to Intravitreal monotherapy in DME as reviewed in many studies<sup>12</sup>, the strategy of combination treatment in DME is becoming more common and as it is controlling more than one pathogenic

factor and the pathogenesis of the macular edema in diabetic patients is multifactorial.

Vascular endothelial growth factor, also known as vascular permeability factor, has been demonstrated to increase retinal vessel permeability by increasing the phosphorylation of tight junction proteins<sup>13</sup>. It was demonstrated recently that retinal hypoxia plays a role in DME, and VEGF, which is upregulated by hypoxia, is likely to contribute to the excessive vascular permeability that results in macular edema in people with diabetes<sup>14</sup>.

Anti-VEGF provides an option to treatment for these patients and it may also be a very useful adjunctive treatment before laser or vitrectomy surgery or a potentially important role as an adjunct to laser in the management of DME<sup>15</sup>.

The role of steroids is mediated through<sup>1</sup> Suppression of VEGF<sup>2</sup> Stabilizing the leakage from retinal vessels<sup>3</sup> Suppression of the release of endothelial cell activators and<sup>4</sup> possibly its anti-inflammatory action<sup>14</sup>. Comparing the response to Intravitreal Triamcinolone versus intravitreal Anti-VEGF is very debatable in terms of improving vision and reducing macular thickness in DME, as some studies proved better response for Anti-VEGF therapy ((studies by Chakrabarti<sup>16</sup> and Mareyand Ellakwa<sup>17</sup>), however, other studies showed superior response for triamcinolone treatment ((Studies of Shimura<sup>18</sup>, Paccola<sup>19</sup>, Isaac<sup>20</sup>, and Lim<sup>20</sup>), and furthermore some other studies (study by Rensch<sup>22</sup>)) revealed comparable effect of Anti-VEGF and triamcinolone in treatment of DME.

In the studies by Chakrabarti<sup>16</sup> and Mareyand Ellakwa<sup>17</sup>, the response to therapy with bevacizumab showed superiority compared with triamcinolone for DME. However, these Studies differed from that of Shimura<sup>18</sup>, Paccola<sup>19</sup>, Isaac<sup>20</sup> and Lim<sup>18</sup>, who demonstrated that Intravitreal triamcinolone was more efficient in reducing DME relative to

bevacizumab, and in the other study by Rensch<sup>22</sup>, IVT and IVB did not differ markedly in term of their effects in improving VA and reducing macular thickness.

We report the results of prospective interventional case series study for a single injection of Ranibizumab monotherapy vs combined therapy of Ranibizumab plus Triamcinolone for the treatment of diabetic macular edema. The results indicate that the combined treatment tolerated well and with few ocular adverse events has reported during the 3 months course of our study. The results indicate that both Ranibizumab monotherapy and combined therapy with triamcinolone was well tolerated with no systemic or ocular adverse events reported in monotherapy group and little side effects reported in combined group during the course of our study. Overall, mean BCVA improved for both the groups from baseline to 6 weeks, when the patients received the injection, this initial 6 weeks improvement was more in combined group and it continued till end of study, but it was maintained between 6 and 12 weeks in monotherapy group Figure 1, This is not surprise as the elimination half-lives of triamcinolone intravitreal injection, would be expected to last for approximately 3 months<sup>21</sup>. While the In human non-vitrectomized eyes, the aqueous half-life of 0.5 mg intravitreally injected Ranibizumab is 7.19 days<sup>24</sup>. The magnitude of changes in the studied OCT parameters; central foveal thickness(CFT) and total macular volume (TMV) were more steep and significant in the combined therapy group and showed maintaining CFT from 6-12 weeks after injection for both groups , while the TMV continue to reduce in combined group from 6-12 weeks Figure 3, and Figure (IV), this finding is correlated with our assumption that the combination of more than one drug might have superior outcome as it would control more than one factor involved in DME pathogenesis

and also the longer half-life of TA. Many studies endorsed that Triamcinolone has side effects with IOP elevation and cataract formation<sup>25-28</sup>. Although most studies have shown a beneficial effect the optional dosage of IVTA is still somewhat confusing. Audren F et al 54 conducted a randomized prospective trial comparing the efficacy of 2 mg Vs 4 mg of Triamcinolone acetonide in the management of diffuse diabetic macular edema. This results showed that there was no dose dependent difference in the response to intervention<sup>29</sup>. In our study, we used 2mg=0.05cc intravitreal triamcinolone so as to reduce the volume related immediate IOP spike as it is combined with 0.05 cc ranibizumab and also to minimize late complications of

high IOP and cataract formation, and we noticed the efficacy is not reduced Figure (I), (III), (IV) and pressure side effects were not significant. (Figure 2), high IOP seen in 7 eyes < 30mmHg and only 2 eyes > 30 mmHg and all are controlled by transient topical antiglaucoma medication and IOP drop down to normal without medication in the 12 weeks visit. Regarding lens status, 10 eyes were Pseudophakic and 2 out remaining 50 eyes have developed cataract Table (IV). Although our follow-up period was too short to provide specific treatment recommendations, the short-term results encourage further prospective studies with different treatment groups and longer follow-up.

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