Egyptian Journal of Medical Research (EJMR)

Comparison of Aflibercept (Eylea®) with Ranibizumab (Lucentis®) in treatment of diabetic macular edema by Optical Coherence Tomography

Hossam El din Khalil, Abdel Rahman Shaaban Ahmed, Hassan Mostafa Mahfouz Eliwa

Department of Ophthalmology, Faculty of Medicine, Beni-Suef University

Abstract:

Background: Diabetic macular edema (DME) can occur at any stage of non-proliferative and proliferative diabetic retinopathy. It is characterized by a swelling of the macular area that normally accounts for high-resolution visual acuity (VA), and DME therefore leads to visual deterioration.

Objective: To compare the effect of Aflibercept (Eylea®) with Ranibizumab (Lucentis®) in treatment of diabetic macular edema by OCT. **Patients and Methods:** This was a prospective comparative study conducted on 32 Diabetic macular edema (DME); to compare the effect of Aflibercept (Eylea®) with Ranibizumab (Lucentis®) in treatment of diabetic macular edema by OCT. **Results:** Pre-operative BCVA had a highly significant positive correlation with post-operative BCVA ($p < 0.0001$). DM duration had a highly significant negative correlation with post-operative BCVA ($p = 0.0002$). Logistic regression analysis shows that; after applying (Forward method) and entering some predictor variables; the decrease in DM duration; had an independent effect on increasing the probability of patient's visual acuity improvement; with significant statistical difference ($p = 0.042$). By using ROC-curve analysis, Aflibercept and Ranibizumab usage showed non-significant predictive values in discrimination of improved patients from patients worsened ones ($p > 0.05$). **Conclusion:** Both aflibercept and ranibizumab improve visual acuity and decrease CMT in eyes with DME and moderate visual loss with no difference between the two drugs.

Keywords: Diabetic macular edema, visual acuity

1. Introduction:

Diabetic macular edema (DME) can occur at any stage of non-proliferative and proliferative diabetic retinopathy. It is characterized by a swelling of the macular area that normally accounts for high-resolution visual acuity (VA), and DME therefore leads to visual deterioration [(1)].

Clinically significant diabetic macular edema (CSMO) is defined as retinal thickening with or without hard exudates within one-disc diameter of the macular center and results in visual impairment when the foveola is involved. This is referred to as CSME with center involvement (CSME-CI) [(2)].

Pathogenesis of DME

One important aspect of the pathophysiology of DME is that cytokine signaling and expression are deregulated in patients with diabetic retinopathy. The permeability of retinal endothelial cells (REC) is controlled by vascular endothelial growth factors (VEGF) and regulated by its binding to the VEGF receptor. DME results from a breakdown of the blood-retinal barrier and leads to retinal thickening caused by an accumulation of fluid and molecules in the retina. The leakage can arise from micro aneurysms or capillaries. The primary endogenous mediator of DME is VEGF, a glycoprotein that is secreted by REC, pericytes and pigment epithelial cells. REC dysfunction seems to be an important step in the development of DME. Hyperglycemia and hypoxia-induced VEGF release are important confounding factors [(3)].

The Early Treatment Diabetic Retinopathy Study (ETDRS) was the first study to provide a treatment paradigm in DME using laser therapy to reduce moderate vision loss by approximately 50% [(4)].

This treatment, however, is destructive and it rather prevents further visual deterioration than improves vision. Therefore, new treatment modalities were developed to overcome the unmet medical need to restore vision. The pathophysiology of DME is rather complex and still not fully understood [(5)].

Various pharmacological compound are under investigation for the treatment of diabetic retinopathy at present. VEGF expression and signaling are deregulated in diabetic retinopathy, and VEGF is a major mediator of blood retinal barrier breakdown and the development of macular edema. Therefore, at present, anti-VEGF treatment is one of the most promising approaches for the treatment of visual loss due to DME [(3)].

Currently, anti-VEGF constitute the preferred initial treatment for DME and include ranibizumab and aflibercept, devacizumab (avastin) As there are no standard protocols or recognized paradigms to follow, the choice of the anti-VEGF is very variable and often subjective relating to the severity of the visual loss suffered by the patient, affordability or availability of the drug, and personal experience of the healthcare provider [(6)].

Diabetic Retinopathy Clinical Research (DRCR) findings and phase III results of VISTA-DME (Study of Intravitreal Administration of VEGF Trap-Eye in Patients with DME)and VIVID-DME (VEGF Trap-Eye in Vision Impairment due to DME)

studies provided strong evidence for aflibercept as an efficient anti-VEGF therapy in DME, yet its use in the low/middle-income countries has been severely limited due to its high cost and its unavailability in some countries [7].

There are 3 anti–vascular endothelial growth factor (anti-VEGF) aflibercept (EYLEA; Regeneron Pharmaceuticals), bevacizumab (Avastin and ranibizumab (Lucentis) for diabetic macular edema (DME) [6].

Aim Of The Work

To compare the effect of Aflibercept (Eylea®) with Ranibizumab (Lucentis®) in treatment of diabetic macular edema by OCT.

2. Patients and Methods:

Design: Prospective, comparative clinical study.

Setting: I-Vision Eye Hospital (for patients' recruitment) and (for intravitreal injections).

Study duration: 6 months.

Patients: A total of 32 eyes were enrolled in the study, to evaluate changes in macular thickness following intravitreal injection of different types of anti-VEGF agents used in patients presenting with diabetic macular edema (DME).

Eligible patients selected according to the following inclusion and exclusion criteria:

Inclusion criteria: Diabetic patients diagnosed according to American Diabetes Association (ADA): A fasting plasma glucose (FPG) level of 126 mg/dL (7.0 mmol/L) or higher, or A 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test (OGTT), or A random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, or A hemoglobin A1c (HbA1c) level of 6.5% (48 mmol/mol) or higher**.** Central foveal thickness (CFT) of more than 300 um

Exclusion criteria: Any systemic disease or vascular insult that causes macular edema, eg (CRVO , BRVO). Any vitro-macular traction.

Patient's randomization: 32 DME eyes included in this study. They were divided into 2 groups: **Aflibercept group (16 patients):** received *Aflibercept (Eylea®) 2 mg (0.05 ml of 40 mg/ml solution)* intravitreal injection. **Ranibizumab group (16 patients):** received *Ranibizumab (Lucentis®) 0.5 mg (0.05 ml of 10 mg/ml solution)* intravitreal injection.

Dose: 0.1 ml of the drug being injected.

Methods:

All patients were subjected to: Full ophthalmologic examination which included history, Snellen visual acuity testing (VA), refraction, slit lamp bio-microscopy, Fundus examination. All of the patients underwent spectral domain optical coherence tomography (OCT) macula before injections, and 6weeks after the injections.

Details of OCT machine: The used machine was (3D OCT 2000 Optical Coherence Tomography machine from TOPCON) machine.

Precaution during intravitreal injection:

Dose: 0.1 ml of the drug being injected.

- Normal IOP
- No eye infection

Possible Complications to be avoided :

- Elevation of IOP
- Central retinal artery occlusion

Main outcome measures:

Measurement of visual acuity to determine the changes in visual acuity, slit lamp examination, refraction, and fundus examination. Central foveal thickness 6 weeks after receiving the injection by OCT.

Ethical considerations:

The nature of the present study and laboratory or radiological procedures was explained to all participants. Consent was obtained from all participants. At the end of the study, all patients were informed about the results of the examinations performed and received appropriate recommendations, and treatment. Approval of ethical committee was taken .

Statistical Methodology:

Sample size: We used OpenEpi (Open Source Epidemiologic Statistics for Public Health) version 3, open source calculator to calculate the sample size **.**

The following criteria were set: A confidence level of 95%, and a margin of error of 5% and exposed outcome by 50% for each treatment, the calculation showed at least 16 participants should be enrolled in each arm (ratio 1:1) with a total Sample size 32 Sample size.

Statistical analysis:

Data entry, processing and statistical analysis was carried out using MedCalc ver. 18.11.3 (MedCalc, Ostend, Belgium). Tests of significance (Mann-Whitney's, Wilcoxon's, Chi square tests, logistic regression analysis, Spearman's correlation, and ROC Curve analysis) were used. Data were presented and suitable analysis was done according to the type of data (parametric and non-parametric) obtained for each variable. P-values less than 0.05 (5%) was considered to be statistically significant.

P- value: level of significance

$P > 0.05$: Non-significant (NS).

$P < 0.05$: Significant (S).

$P < 0.01$: Highly significant (HS).

Descriptive statistics: Mean, Standard deviation (± SD) and range for parametric numerical data, while Median and Inter-quartile range (IQR) for non-parametric numerical data. Frequency and percentage of non-numerical data.

Analytical statistics: Mann-Whitney's Test (U test) was used to assess the statistical significance of the difference of a non-parametric variable between two study

groups. Wilcoxon's test was used to assess the statistical significance of the difference of a non-parametric variable between two (paired) study group means. Chi-Square test was used to examine the relationship between two qualitative variables. Correlation analysis (using Spearman's method): To assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically "r" defines the strength and direction of the linear relationship between two variables. Logistic regression: useful in the prediction of the presence or absence of an outcome based on a set of independent variables. It is similar to a linear regression model but is suited when the dependent variable is qualitative (categorical). The ROC Curve (receiver operating characteristic) provides a useful way to evaluate the Sensitivity and specificity for quantitative Diagnostic measures that categorize cases into one of two groups. Excellent accuracy = 0.90 to 1 (%). Good accuracy = 0.80 to 0.90 (%). Fair accuracy = 0.70 to 0.80 (%). Poor accuracy = 0.60 to 0.70 (%). Failed accuracy = 0.50 to 0.60 (%)

3. Results:

Table 1: Basic clinical and ophthalmic data among 32 DME patients:

Variables		**Frequency (%)**
Age (years)		56 ± 7.87*
DM duration (year)		13.18 ± 3.7
Gender	Female	18 (56.2%)
	Male	14 (43.8%)

** Mean ± SD.*

Table 2: Pre-operative ophthalmic assessment among 32 DME patients:

Variables		**Frequency (%)**
IOP (mmHg)		17.6 ± 2.3
BCVA (Log Mar)		0.12 ± 0.09
Central Macular Thickness (um)		412.28 ± 137.86
Fundus examination	Diabetic macular edema	32 (100%)

IOP: intra-ocular pressure, BCVA: Best Corrected Visual Acuity.

Table 3: Post-operative ophthalmic assessment among 32 DME patients:

Variables	Frequency (%)
IOP (mmHg)	17.9 ± 1.82
BCVA (Log Mar)	0.25 ± 0.13
Central Macular Thickness (um)	307.96 ± 122.6

Table 4: Visual acuity outcome data among 32 DME patients:

Variables		Frequency (%)
Visual acuity outcome	Worsened	6 (18.8%)
	Improved	26 (81.2%)

Table 5: Comparison between the 2 groups as regards basic clinical and ophthalmic data using Mann-Whitney's U and Chi square tests:

Variable		Aflibercept group (16)	Ranibizumab group (16)	Mann-Whitney's U test
		Median (IQR)	Median (IQR)	P value
Age (years)		53 (48.5 – 61.5)	56.5 (53 – 60.5)	= 0.2820
DM duration (year)		12.5 (11 – 14.5)	13 (10.5 – 15.5)	= 0.8646
Variable		**Aflibercept group (16)**	**Ranibizumab group (16)**	**Chi square test**
				P value
Gender	Female	10 (62.5%)	8 (50%)	= 0.4830
	Male	6 (37.5%)	8 (50%)	

*IQR: inter-quartile range. * Percentage of Column Total.*

Table 6: Comparison between the 2 groups as regards pre-operative ophthalmic assessment using Mann-Whitney's U test:

Variable	Aflibercept group (16)	Ranibizumab group (16)	Mann-Whitney's U test
	Median (IQR)	Median (IQR)	P value
IOP (mmHg)	17 (15.5 – 19)	18 (17 – 19.5)	= 0.3225

BCVA (Log Mar)	0.1 (0.05 – 0.11)	0.1 (0.05 – 0.18)	= 0.8161
Central Macular Thickness (um)	382 (327 – 500)	317 (311 – 442)	= 0.0896

Table 7: Comparison between the 2 groups as regards post-operative ophthalmic assessment using Mann-Whitney's U test:

Variable	**Aflibercept group (16)**	**Ranibizumab group (16)**	**Mann-Whitney's U test**
	Median (IQR)	**Median (IQR)**	**P value**
IOP (mmHg)	17.5 (16 – 20)	18 (17 – 19)	= 0.8041
BCVA (Log Mar)	0.25 (0.16 – 0.4)	0.25 (0.15 – 0.32)	= 0.6079
Central Macular Thickness (um)	252 (215 – 350)	303 (217 – 381)	= 0.4738

Table 8: Comparison between the 2 groups as regards visual acuity outcome data using Chi square test:

Variable		**Aflibercept group (16)**	**Ranibizumab group (16)**	**Chi square test**
				P value
Visual acuity outcome	Worsened Improved	2 (12.5%) 14 (87.5%)	4 (25%) 12 (75%)	= 0.3726

*** Percentage of Column Total.**

Table 9: Comparison between 32 DME patients as regards serial ophthalmic assessments:

Aflibercept group	**Pre-operative assessment**	**Post-operative assessment**	**Wilcoxon's test**
	Median (IQR)	**Median (IQR)**	**P value**
IOP (mmHg)	17 (15.5 – 19)	17.5 (16 – 20)	= 0.3575
BCVA (Log Mar)	0.1 (0.05 – 0.11)	0.25 (0.16 – 0.4)	= 0.0001**
Central Macular Thickness (um)	382 (327 – 500)	252 (215 – 350)	< 0.0001**
Ranibizumab group	**Pre-operative assessment**	**Post-operative assessment**	**Wilcoxon's test**
	Median (IQR)	**Median (IQR)**	**P value**
IOP (mmHg)	18 (17 – 19.5)	18 (17 – 19)	= 0.6788
BCVA (Log Mar)	0.1 (0.05 – 0.18)	0.25 (0.15 –	= 0.0005**

		0.32)	
Central Macular Thickness (um)	317 (311 – 442)	303.5 (217 – 381)	= 0.015*

Table 10: Spearman's correlation analysis for baseline clinical / pre-operative Factors associated with post-operative BCVA:

Associated Factor	Post-operative BCVA	
	rho	P
Age (years)	-0.0833	=0.6504
DM duration (year)	-0.608	=0.0002**
Pre-operative IOP (mmHg)	0.0163	=0.9293
Pre-operative BCVA (Log Mar)	0.664	<0.0001**
Pre-operative Central Macular Thickness (um)	-0.292	=0.1050

rho: Spearman's rho (correlation coefficient).

Table 11: Logistic regression model for the Factors affecting patient's visual acuity improvement using Forward method:

Predictor Factor	Coefficient	OR	P value
(Constant)			
DM duration	-0.26850	0.7645	0.042*

Other factors excluded from the model as (p value > 0.1). OR: odds ratio.

Table 12: Roc-curve of each drug to predict patient's visual acuity improvement:

Variable	AUC	Sensitivity (%)	Specificity (%)	P value
Aflibercept	0.553	93.75	18.75	0.6120
Ranibizumab	0.563	25	78.5	0.5433

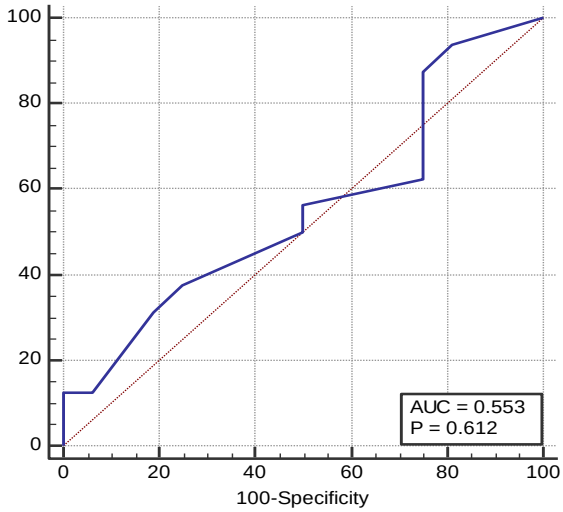

Figure 1: ROC curve of Aflibercept (patient's visual acuity improvement).

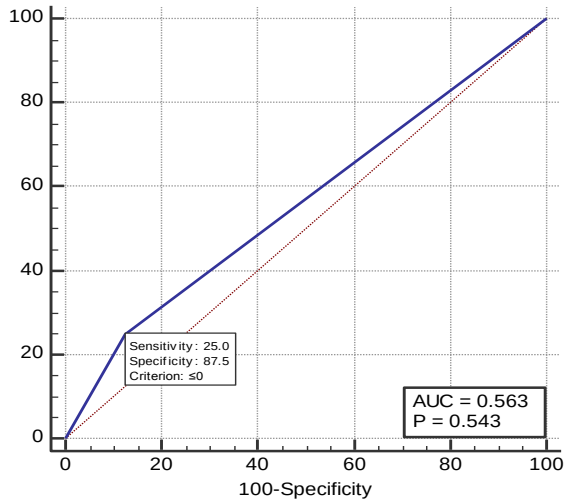

Figure 2: ROC curve of Ranibizumab (patient's visual acuity improvement).

ROC (Receiver operating characteristic), AUC= Area under curve, SE= Standard Error.

4. Discussion:

This was a prospective comparative study conducted on 32 Diabetic macular edema (DME); to compare the effect of Aflibercept (Eylea®) with Ranibizumab (Lucentis®) in treatment of diabetic macular edema by OCT.

We found that; the mean age of all patients (56 ± 7.87) years, and the mean DM duration was (13.18 ± 3.7) years. Regarding gender of the patients, (56.2%) of patients were females; while (43.8%) were males. Which came in agreement with ***Fauser & Muether*** [(8)]***, Babiuch et al. , 2019, Hykin et al.*** [(10)]***, Khurana et al.*** [(11)]**.**

Babiuch et al. reported that, Data was collected on 20 unique patients from baseline to 6 months. The mean age was 63.7 (range, 45–78) years, and 13 patients (65%) were female [(9)]**.**

Hykin et al. reported that, Between December 12, 2014, and December 16, 2016, 587 patients were assessed for eligibility and 463 were randomly assigned and allocated to receive ranibizumab (n = 155), aflibercept (n = 154), or bevacizumab (n = 154). Of 463 total participants, 198 (42.8%) were female, with a mean (SD) age of 69.1 (13.0) years [(10)]**.**

Khurana et al. reported that, twenty patients were enrolled between June 2013 and August 2014. At baseline, the mean age was 64

years (range, 38e88 years) and 50% (10/20) were women [11].

Fouda & Bahgat reported that, a total of 70 eyes of 42 patients received intraocular injections of aflibercept (group I, 35 eyes) or intraocular injections of ranibizumab (group II, 35 eyes). The mean age of the patients was 55.05±4.7 years (range: 45–65 years) in aflibercept group and 56.64±5.8 years (range: 42–68 years) in ranibizumab group [12].

Network reported that, Between August 22, 2012, and August 28, 2013, 660 participants were randomly assigned to receive aflibercept (224 participants), bevacizumab (218), or ranibizumab (218). The mean age of the participants was 61±10 years [13].

Regarding pre-operative ophthalmic assessment; the average IOP of all patients was (17.6 ± 2.3) mmHg, the average BCVA was (0.12 ± 0.09) log Mar, and the average central macular thickness was (412.28 ± 137.86) um. Which came in agreement with ***Strong et al. [14], Babiuch et al. [9], Plaza-Ramos et al. [15], Khurana et al. [11].***

Strong et al. reported that, on examination, BCVA was 6/18 in the right eye and 6/36 in the left eye. Visual field testing to confrontation revealed constricted fields of 10–20 degrees in both eyes. Spectral domain optical coherence tomography (SDOCT) showed marked bilateral CMO with central macular thickness (CMT) of 394 and 414 μm in the right and left eye, respectively [14].

Babiuch et al. reported that, the mean baseline BCVA was 70 ± 7.2 (60–81) letters (≅ 20/40). The mean CST upon study entry was 419.7 ± 92 (328– 585) μm [9].

Plaza-Ramos et al. reported that, Basal BCVA was 0.55 (+/- 0.35) in the ranibizumab-treated group and 0.48 (+/-0.29) in the aflibercept-treated group (P = 0.109). Central macular thickness (CMT) was 483.45 (+/-142.13) μm in the ranibizumab-treated group and 419.46 (+/-104.61) μm in the aflibercept- treated group (P<0.001) [15].

Khurana et al. reported that, at baseline, the mean visual acuity was 20/63 (range, 20/25 to 20/200) and the retinal thickness was 551 mm (range, 232e781 mm) [11].

Fouda & Bahgat reported that, the mean baseline BCVA and CMT of eyes treated with aflibercept were 0.17±0.05 and 465.29±33.7 μm and of eyes treated with ranibizumab were 0.18±0.04 and 471.5±34.4 μm, respectively [12].

Network reported that, the mean visual acuity letter score at baseline was 64.8±11.3 (Snellen equivalent, approximately 20/50), and the mean central subfield thickness was 412±130 μm. Baseline characteristics were similar in the three groups [13].

Regarding post-operative ophthalmic assessment; the average IOP of all patients was (17.9 ± 1.82) mmHg, the average BCVA was (0.25 ± 0.13) log Mar, and the average

central macular thickness was (307.96 ± 122.6) um. Which came in agreement with ***Plaza-Ramos et al.*** [15], ***Fouda & Bahgat*** [12], ***Babiuch et al.*** [9], and ***Lang*** [3].

Plaza-Ramos et al. reported that, With regard to BCVA, we can appreciate baseline overall BCVA was 0.52 (+/-0.34) log MAR, BCVA at 4th month visit was 0.40 (+/-0.31) log MAR, and BCVA at the end of the study was 0.40 (+/-0.33) log MAR [15].

Fouda & Bahgat reported that, The BCVA was recorded monthly for 1 year after the last loading injection. At the end of the follow-up period, the mean BCVA in eyes treated with aflibercept improved to 0.42±0.28 and that in eyes treated with ranibizumab improved to 0.37±0.23 [12].

Babiuch et al. reported that, Mean BCVA at the 6 months visit prior to enrollment and drug switch was 70.1 ± 7.7 and at baseline was 70.0 ± 7.2 (p = 0.95). BCVA increased minimally between the baseline visit and 6 month [9].

Lang reported that, primary endpoint was the change in BCVA at the end of the follow-up. At month 12, mean BCVA had improved by 10.3 letters [3].

Regarding visual acuity outcome data; (81.2%) of DME patients improved, while (18.8%) of patients had worsened condition. Which came in agreement with ***Khurana et al.*** [11], ***Hykin et al.*** [10], ***Moustafa & Moschos*** [16].

Khurana et al. reported that, at baseline, the mean BCVA was 62 ± 18 letters (20/63 Snellen equivalent). The mean visual acuity improved 6 ETDRS letters with IAI by week 52 from baseline (P = 0.02) to 68 ± 20 letters (20/40 Snellen equivalent). Of note, 1 patient had severe vision loss (38 letters) after developing a combined macular hole and rhegmatogenous retinal detachment 11 weeks after IAI. At the week 52 visit, 77% of patients (13/17) had a BCVA of 20/40 or better (compared with 53% [9/17 patients] at baseline). The individual changes in BCVA for the 17 patients who completed the week [11].

Hykin et al. reported that, the primary outcome was the change in BCV A letter score from baseline to 100 weeks in the study eye for each intervention compared with ranibizumab. Secondary outcomes in the study eye included a gain of at least 10 BCVA letters at 52 weeks and at least 15 BCVA letters at 100 weeks, losses of 15 or fewer at 52 weeks or at least 30 BCVA letters at 100 weeks, change in OCT CST from baseline to 52 and to 100 weeks, OCT CST less than 320 μm at 52 and 100 weeks, and the number of injections by 100 weeks. Adverse events were recorded throughout 100 weeks [10].

Moustafa & Moschos reported that, one month after treatment, BCVA in the right eye elevated to 4/10 and macular edema had apparently improved, as it is depicted in the respective OCT scan [16].

Wells et al. reported that, Visual acuity at the 2-year visit improved from baseline, on average, by 12.8 letters with aflibercept, 10.0 letters with bevacizumab, and 12.3 letters with ranibizumab ***(17)*.**

Klein et al. reported that, six months prior to switch to IAI, the Snellen visual acuity ranged from 20/25 to 20/100. Over the 6 months prior to switch to IAI, the Snellen visual acuity declined in 8 patients (73%), improved in 2 patients (18%), and remained unchanged in 1 patient (9%). At time of switch to IAI, the Snellen visual acuity ranged from 20/40 to 20/200. Six months after switch to IAI ***(18)*.**

Comparative study between the 2 groups revealed non-significant difference as regards post-operative IOP, BCVA and central macular thickness (p > 0.05). Which came in agreement with ***Babiuch et al.*** ***(9)*, *Plaza-Ramos et al.*** ***(15)*, *Fouda & Bahgat*** ***(12)*.**

Babiuch et al. reported that, Mean BCVA at the 6 months visit prior to enrollment and drug switch was 70.1 ± 7.7 and at baseline was 70.0 ± 7.2 (p = 0.95). BCVA increased minimally between the baseline visit and 6 months, 70.0 ± 7.2 (60–81) to 71.5 ± 8.9 (54–83), but this change was not statistically significant (p = 0.38) ***(9)***.

Plaza-Ramos et al. ***(15)*** reported that, with regard to the comparison between the ranibizumab-treated group and the aflibercept treated group, we can see that BCVA at 4th month visit was 0.41 (+/- 0.34) log MAR in patients treated with ranibizumab and 0.40 (+/- 0.27) log MAR in those treated with aflibercept (P = 0.888). At the end of the study, BCVA remained at 0.40 (+/- 0.35) log MAR in the ranibizumab group, and at 0.40 (+/- 0.29) log-Mar (P = 0.864) in the patients treated with aflibercept ***(15)*.**

Fouda & Bahgat reported that, The BCVA was recorded monthly for 1 year after the last loading injection. At the end of the follow-up period, the mean BCVA in eyes treated with aflibercept improved to 0.42±0.28 and that in eyes treated with ranibizumab improved to 0.37±0.23 with no significant difference between the two groups (P=0.27) ***(12)*.**

Comparative study between the 2 groups revealed; slight increase in visual acuity improvement in Aflibercept (Eylea®) group (78.5%); compared to Ranibizumab (Lucentis®) group (75%), without reaching statistical significance (p > 0.05). Which came in agreement with ***Strong et al.*** ***(14)*, *Régnier et al.*** ***(19)*, *Hykin et al.*** ***(10)*, *Fouda & Bahgat*** ***(12)*,** and ***Network*** ***(13)*.**

Régnier et al. reported that, it was assumed that the frequency of AEs for ranibizumab and aflibercept was equal. However, in the VIVID-DME and VISTA-DME studies, five of 287 (1.7%) patients in the aflibercept 2q8 group experienced ocular serious AEs ***(19)***.

Hykin et al. reported that, the mean (SD) gain in the BCVA letter score was 12.5 (21.1) for ranibizumab, 15.1 (18.7) for

aflibercept, and 9.8 (21.4) for bevacizumab at 100 weeks (Figure 2A). The ITT primary outcome at 100 weeks showed that bevacizumab was not non inferior compared with ranibizumab. However, aflibercept was non inferior but not superior to ranibizumab [(10)].

Fouda & Bahgat reported that, Aflibercept and ranibizumab have the same efficacy in the treatment of DME in eyes with moderate visual loss but with less number of drug re-injection and less treatment burden with aflibercept (2.62±0.68 versus 3.03±0.95) [(12)].

Network reported that, the mean improvement in the visual-acuity letter score at 1 year was greater with aflibercept than with bevacizumab or ranibizumab (13.3 vs. 9.7 and 11.2, respectively; P<0.001 for aflibercept vs. bevacizumab and P = 0.03 for aflibercept vs. ranibizumab) [(13)].

Spearman's correlation analysis shows that; pre-operative BCVA had a highly significant positive correlation with post-operative BCVA (p < 0.0001). Which came in agreement with ***Plaza-Ramos et al.*** [(15)], ***Hykin et al.*** [(10)].

Plaza-Ramos et al. reported that, we performed a comparison between patients in both groups according to their basal BCVA in log MAR. Patients with 0.4 log MAR or higher values were clustered in the group known as the bad BCVA group. On the contrary, patients with lower basal values of 0.4 log MAR BCVA were considered to be part of the good BCVA group. Patients in the group with good BCVA at baseline started out with 0.24 (+/- 0.78) log MAR, whereas the bad BCVA group started out with 0.69 (+/- 0.32) log MAR (P<0.001) [(15)].

Hykin et al. reported that, the mean (SD) visual gains by 24 weeks from baseline were 11.4 (19.3) in the ranibizumab group, 13.4 (16.4) in the aflibercept group, and 10.4 (16.6) in the bevacizumab group. The mean BCVA letter score at week 24 decreased by approximately 3 letters across groups after pro Renata (PRN) injections at weeks 16 and 20. Fewer injections were given at those times (total for ranibizumab injections, 123; aflibercept, 76; and bevacizumab, 121), but the number of injections increased gradually thereafter across groups to week 100, during which period patients were seen every 4 to 8 weeks and injected promptly if retreatment criteria were met [(10)].

Spearman's correlation analysis shows that; DM duration had a highly significant negative correlation with post-operative BCVA (p = 0.0002). Which came in agreement with ***Lang*** [(3)].

Lang [(3)] reported that, the prevalence of visual impairment due to DME is estimated to be 5.4% in Europe. Vascular endothelial growth factor (VEGF) is overexpressed in diabetic eyes and plays a key role in the development of DME. VEGF levels were

proven to be elevated in the vitreous and retina in patients with diabetic retinopathy [(3)].

By using ROC-curve analysis, Aflibercept and Ranibizumab usage showed non-significant predictive values in discrimination of improved patients from patients worsened ones ($p > 0.05$).Which came in agreement with ***Babiuch et al.*** [(9)]**,** ***Fauser & Muether*** [(8)]**,** ***Heier et al.*** [(6)]**,** ***Plaza-Ramos et al.*** [(15)]**,** ***Hykin et al.*** [(10)]**.**

Babiuch et al. reported that, Prospective data is also available and most studies reported no visual improvement despite a significant universal reduction in the CST. A pos-hoc analysis of VIVID/VISTA trials reported that the rise in visual acuity is gradual, and visual acuity peak is only established after 6–9 months of treatment or longer. This study reports no difference in FAZ area after 6 months treatment with IAI. Outcomes of other reports on effects of chronic anti-VEGF therapy on FAZ area are contradictory [(9)].

Fauser & Muether reported that, Clinical impression suggests that the difference between the two drugs is smaller than the VSTs would imply. However, the fact that clinical activity can occur at a time point as early as 50% of the individual VST reduces the absolute difference in days between the two drugs also by a factor of 2. Furthermore, patients are usually not evaluated in intervals of less than 4 weeks, which overestimates the drug duration in some patients treated with ranibizumab. All this explains the discrepancy between the clinical experience and the true clinical effect between the two drugs [(8)]**.**

Heier et al. reported that, the substantial variation in the costs of these agents is important to patients, health care professionals, insurance companies, health care programs, and governments. In situations in which patients have access to aflibercept and demonstrate ocular findings similar to the patient inclusion criteria used in this RCT, the results suggest that worse visual acuity at the time anti-VEGF therapy is initiated is associated with greater treatment benefit on average with aflibercept rather than bevacizumab or ranibizumab. If a patient does not have access to aflibercept, initiating therapy with bevacizumab is a reasonable consideration. With access to adequately repackaged bevacizumab, many authors would initiate therapy with bevacizumab when visual acuity is good (i.e., 20/32 to 20/40as measured by the DRCR Network), the rationale recognizes that the cost effectiveness of bevacizumab far outweighs that of aflibercept or ranibizumab. On average, no differences in visual acuity outcomes at 1 year have been identified among the 3 anti-VEGF agents when initiating therapy at better levels of visual acuity [(6)].

Plaza-Ramos et al. reported that, statistics proved that baseline BCVA is not different between ranibizumab and aflibercept groups ($P = 0.109$). The ranibizumab-treated

group had a baseline BCVA of 0.55 (+/-0.35) log MAR and the aflibercept-treated one had a baseline BCVA of 0.48 (+/- 0.29) log MAR. An important issue to take into account is the difference between the numbers of naive patients in both groups [(15)].

Hykin et al. reported that, the proportion of patients across groups with at least 15 BCVA letter gain (ranibizumab, 47%; aflibercept, 52%; and bevacizumab, 45%) was similar, and no group had more than 6% of patients with a loss of at least 30 BCVA letters a week 100. There were no statistically significant differences across groups in the proportion of patients with at least 10 BCVA letter gain or less than 15 BCVA letters loss [(10)].

5. Conclusion:

Both aflibercept and ranibizumab improve visual acuity and decrease CMT in eyes with DME and moderate visual loss with no difference between the two drugs.

6. References:

1. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, Chen SJ, Dekker JM, Fletcher A, Grauslund J, Haffner S (2012): Global prevalence and major risk factors of diabetic retinopathy. Diabetes care. 35(3):556-64.
2. Mansour AM, Dedhia C, Chhablani J (2017): Three-month outcome of intravitreal ziv-aflibercept in eyes with diabetic macular oedema. *British Journal of Ophthalmology*, *101*(2): 166-169.
3. Lang GE (2012): Diabetic macular edema. *Ophthalmologica*, *227*(Suppl. 1): 21-29.
4. Bhagat N, Grigorian RA, Tutela A, Zarbin MA (2009): Diabetic macular edema: pathogenesis and treatment. *Survey of ophthalmology*, *54*(1): 1-32.
5. Jampol LM, Bressler NM, Glassman AR (2014): Revolution to a new standard treatment of diabetic macular edema. *Jama*, *311*(22): 2269-2270.
6. Heier JS, Bressler NM, Avery RL, Bakri SJ, Boyer DS, Brown DM, Dugel PU, Freund KB, Glassman AR, Kim JE (2016): Comparison of aflibercept, bevacizumab, and ranibizumab for treatment of diabetic macular edema: Extrapolation of data to clinical practice. *JAMA Ophthalmology*, *134*(1): 95–99.
7. Brown DM, Schmidt-Erfurth U, Do DV, Holz FG, Boyer DS, Midena E, Heier JS, Terasaki H, Kaiser PK, Marcus DM, Nguyen QD (2015): Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. Ophthalmology. 122(10):2044-52.
8. Fauser S & Muether PS (2016): Clinical correlation to differences in ranibizumab and aflibercept vascular endothelial growth factor suppression times. *British Journal of Ophthalmology*, *100*(11): 1494–1498.

9. Babiuch AS, Conti TF, Conti FF, Silva FQ, Rachitskaya A, Yuan A, Singh RP (2019): Diabetic macular edema treated with intravitreal aflibercept injection after treatment with other anti-VEGF agents (SWAP-TWO study): 6-month interim analysis. *International Journal of Retina and Vitreous*, *5*(1): 17.
10. Hykin P, Prevost AT, Vasconcelos JC, Murphy C, Kelly J, Ramu J, Hounsome B, Yang Y, Harding SP, Lotery A (2019): Clinical effectiveness of intravitreal therapy with ranibizumab vs aflibercept vs bevacizumab for macular edema secondary to central retinal vein occlusion: A randomized clinical trial. *JAMA Ophthalmology*, *137*(11): 1256–1264.
11. Khurana RN, Chang LK, Bansal AS, Palmer JD, Wu C, Wieland MR (2018): Aflibercept for previously treated macular edema associated with central retinal vein occlusions: 1-year results of the NEWTON Study. *Ophthalmology Retina*, *2*(2): 128–133.
12. Fouda SM & Bahgat AM (2017): Intravitreal aflibercept versus intravitreal ranibizumab for the treatment of diabetic macular edema. *Clinical Ophthalmology (Auckland, NZ): 11*, 567.
13. Network DRCR (2015): Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *New England Journal of Medicine*, *372*(13): 1193–1203.
14. Strong SA, Gurbaxani A, Michaelides M (2016): Treatment of retinitis pigmentosa-associated cystoid macular oedema using intravitreal aflibercept (Eylea) despite minimal response to ranibizumab (Lucentis): A case report. *Case Reports in Ophthalmology*, *7*(2): 389–397.
15. Plaza-Ramos P, Borque E, García-Layana A (2019): Evaluation of ranibizumab and aflibercept for the treatment of diabetic macular edema in daily clinical practice. *PLoS One*, *14*(10): e0223793.
16. Moustafa GA & Moschos MM (2015): Intravitreal aflibercept (Eylea) injection for cystoid macular edema secondary to retinitis pigmentosa-a first case report and short review of the literature. *BMC Ophthalmology*, *15*(1): 1–6.
17. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, Brucker AJ, Ferris FL, Hampton GR, Jhaveri C (2016): Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: Two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology*, *123*(6): 1351–1359.
18. Klein KA, Cleary TS, Reichel E (2017): Effect of intravitreal aflibercept on recalcitrant diabetic macular edema. *International Journal of Retina and Vitreous*, *3*(1): 16.
19. Régnier SA, Malcolm W, Haig J, Xue W (2015): Cost-effectiveness of ranibizumab versus aflibercept in the treatment of visual

impairment due to diabetic macular edema: A UK healthcare perspective. *ClinicoEconomics and Outcomes Research: CEOR*, *7*, 235.