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Effect of Monocular Intravitreal Anti-Vascular Endothelial Growth Factor Injection on the Fellow Eye

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ABSTRACT

Background: The contralateral effect of intravitreal Anti-Vascular Endothelial Growth Factor (anti- VEGF) on the fellow eye is still controversial.

Objectives: The aim of the current work was to evaluate the contralateral effect of anti-VEGF injection on the fellow eye in patients with bilateral diabetic macular edema (DME).

Patients and Methods: This prospective interventional study included a total of 30 female patients with bilateral DME aged from 30 to 70 years, attending at Department of Ophthalmology, International Medical Center, Armed Forces. This study was conducted to assess the effect of unilateral intravitreal injection of anti-VEGF on the fellow eye. It was conducted between 2018 to 2019.

Results: The mean age ± SD was 61.0 ± 7.8 years and duration of DM was 17.50 ± 9.797 years. All patients were obese with mean body mass index (BMI) 37.3 ± 3.5. 21 cases were hypertensive, 2 patients had albuminuria. Statistically significant decrease in central retinal thickness (CRT) in both eyes were found with mean ± SD reduction 83.07 ± 31.67 µm in injected eye and 11.30 ± 12.78 µm in the untreated eye from baseline, no significant improvement in best corrected visual acuity (BCVA). There was no significance correlation between hypertension and improvement in CRT, while the patients with albuminuria showed worsening in CRT in untreated eye.

Conclusion: It could be concluded that ranibizumab can escape into the systemic circulation and reduce contralateral CRT and the systemic condition could affect the outcome of the treatment.

Keywords: DME, anti-VEGF, fellow eye.

INTRODUCTION

The incidence of diabetic retinopathy including diabetic macular edema (DME) which is the most common microvascular complication of DM, increased to alarming level and it considered the major causes of severe visual impairment in DM along with [(1)].

Vitreous VEGF levels which is an important mediator in DM has been observed to be high in DME, using VEGF inhibitors (anti-VEGF) was believed to be beneficial in reversing the loss of vision caused by macular edema. Trials have handled the efficacy and safety of different types of anti-VEGF in the treatment of DME, including Pegaptanib, ranibizumab, bevacizumab, and aflibercept [(2)].

However, the observation of fellow eye effects, along with the pharmacokinetic studies showing concentrations of the agents in the bloodstream correlating with reduction in circulating free VEGF levels, provide biologic possibility of potential systemic effects of these agents [(3)].

So, it is suggested that anti-VEGF agents reach the untreated eye through the systemic circulation [(4)], but the potential effect of unilateral injection of anti- VEGFs in the fellow eye is still doubtful in spite of some case reports of therapeutic effects after monocular injection of anti-VEGFs in the fellow eye [(5)].

The aim of the current work was to evaluate the contralateral effect of anti-VEGF injection on the fellow eye in patients with bilateral diabetic macular edema (DME).

PATIENTS AND METHODS

This prospective interventional study included a total of 30 female patients with bilateral DME aged from 30 to 70 years, attending at Department of Ophthalmology, International Medical Center, Armed Forces. This study was conducted to assess the effect of unilateral intravitreal injection of anti-VEGF on the fellow eye. This study was conducted between 2018 to 2019.

Ethical approval:

Approval of the ethical committee was obtained. Written informed consent from all the subjects were obtained.

The inclusion criteria were diabetic patients with bilateral diabetic macular edema. The exclusion criteria were previous history of cataract surgeries in last six months, eyes with optic nerve pathology, previous macular edema treated by laser or anti-VEGF injections, previous history of subtenon or intraocular steroid injection, Presence of other retinal diseases and previous history of vitreo-retinal surgeries.

Full ophthalmic and medical history were taken. All patients were subjected to Full ophthalmological examination, visual acuity by snellen chart, pupils

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examination, intraocular pressure (IOP) measurement with Goldman applanation tonometer, Slit-lamp examination and Fundoscopic examination. Along with, color test by using Ishihara plats and Amselar grid test.

CRT measurement was performed bilaterally by spectral domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany), after appropriate pupillary dilatation using cyclopentolate 1% eye drops.

Systemic work up had done for patients before the injection including: BMI, fasting and postprandial serum glucose level that did not exceed 150 mg/dl for fasting and 200 mg/dl for postprandial, HbA_{1C}, Control hypertension so the systolic blood pressure did not exceed 140 mmHg and diastolic blood pressure 90 mmHg, INR was done before the injection and had to be within normal range, anticoagulant/ antiplatelet agents was stopped before the injection for at least 3 days, liver and kidney functions and CBC.

All patients were scheduled to receive 1 intravitreal injection of 0.5 mg ranibizumab. Intravitreal injections were performed in the eye exhibiting more severe macular edema, which was determined by the central thickness and visual acuity.

All intravitreal injections were performed according to a standard protocol at the operation theater. 4 weeks after the injection same systemic laboratory investigations, BCVA and OCT were repeated.

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.
- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. 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

Thirty female patients suffering from DM were enrolled into this study with bilateral NPDR with macular edema received single injection in the worst eye. We chose patients with normal systemic lab investigations pre-injection ranges as demonstrated in table (1).

Table (1): Baseline demographics and ocular characteristics of patients pre and post injection:

	Mean ± SD	
	Pre-injection	**Post-injection**
Age (years)	61.0 ± 7.8	
Duration of DM (years)	17.50 ± 9.797	
Body mass index (kg/m^2)	37.3 ± 3.5	
HbA1c (%)	7.37 ± 0.399	
hemoglobin (g/dl)	11.93 ± 0.455	11.90 ± 0.430
Kidney functions		
Urea (mg/dl)	22.57 ± 7.001	23.30 ± 7.091
Creatinine (mg/dl)	0.82 ± 0.137	0.85 ± 138
Liver functions		
SGOT (U/L)	20.73 ± 5.311	21.60 ± 5.150
SGPT (U/L)	25.80 ± 6.266	26.47 ± 6.067
INR	1.01 ± 0.19	1.01 ± 0.037
Fasting serum sugar (mg/dl)	96.00 ± 8.400	123.67 ± 22.350
Post prandial serum sugar(mg/dl)	123.67 ± 22.350	129.73 ± 8.043
IOP (mmHg)	RT 12.50 ± 2, LT 12.7 ± 2.4	RT 13.2 ± 1.7, LT 13.5 ± 2.1

We divided our patients into 3 groups as showed in table (2), 2 cases of group 3 were having positive albuminuria in urine analysis.

Table (2): Distribution of cases according to the change in CRT of the fellow eye:

	Change in fellow eye's CRT		Number of cases
Group 1	Improved	Decreased > 10 µm	17
Group 2	Stable	± 10 µm	10
Group 3	Worsened	Increased > 10 µm	3

Statistically significant changes were found after injection in both eyes the mean CRT of injected eye preinjection was 432.63 ± 107.158 µm and decreased significantly post injection to 349.57 ± 99.910 µm with mean reduction 83.07 ± 31.67µm, The mean CRT of fellow eye preinjection348.90 ± 97.431 µm and became 336.93 ± 97.060 µm post injection with mean reduction in CRT 11.30 ± 12.78 µm as showed in figures (1) and tables (2, 3,4,5).

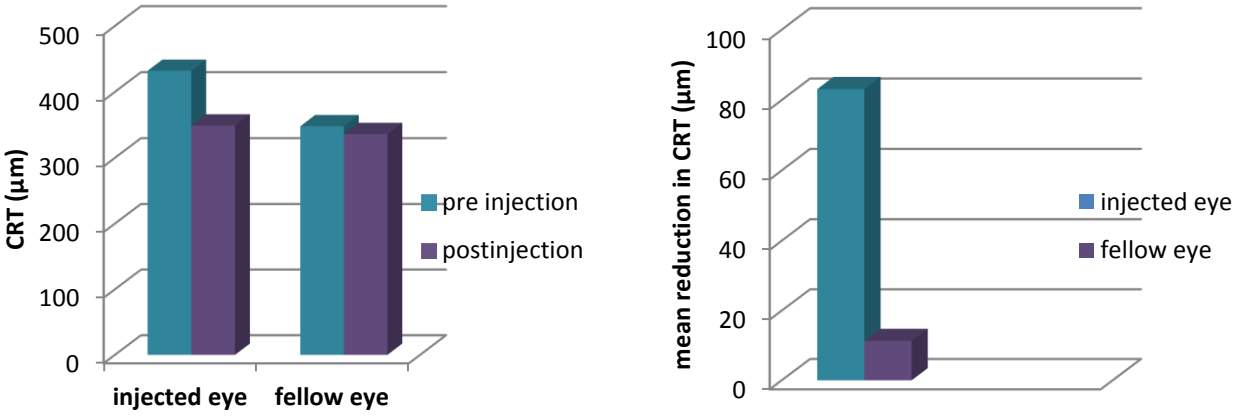

Figure (1): shows the improvement in CRT of both eyes post-injection (the chart on the left) and the correlation between the mean reduction of CRT of both eyes (the chart on the right).

Table (3): The mean improvement in CRT of injected eye and it's significance.

		Mean ± SD	T	P value
Injected eye	**Pre-injection**	432.63 ± 107.158 µm	29	0.0001
	Post-injection	349.57 ± 99.910 µm		

Table (4): The mean improvement in CRT of fellow eye and it's significance.

		Mean ± SD	T	P value
Fellow eye	**Pre-injection**	348.90 ± 97.431 µm	29	0.0001
	Post-injection	336.93 ± 97.060 µm		

Table (5): the mean reduction of CRT in both eyes:

	Injected eye	Fellow eye
Mean ± SD	83.07 ± 31.67	11.30 ± 12.78

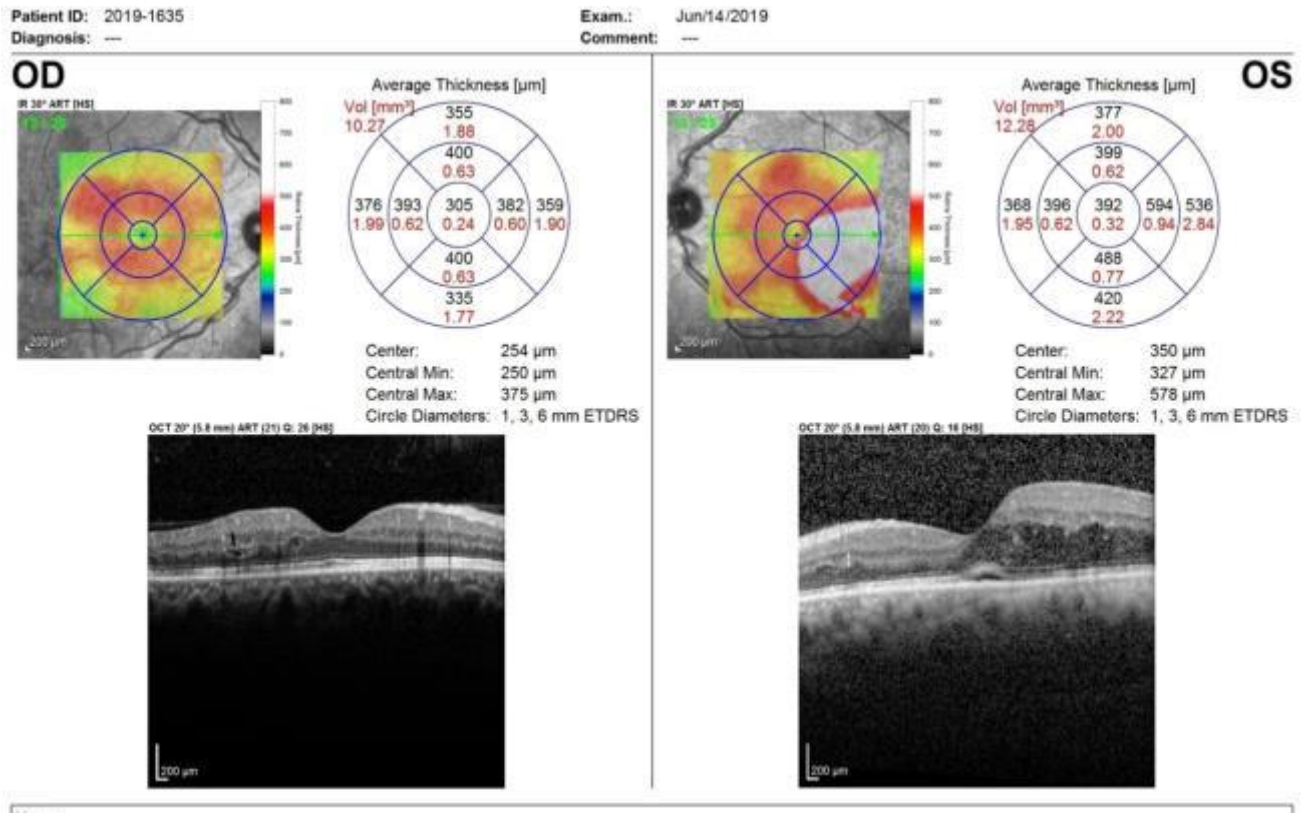

Figure (2): case no.1 (group 1) showing bilateral cystoid diabetic macular edema pre-injection, the BCVA was 6/9 and 6/36 by snellen chart for right and left eye respectively.

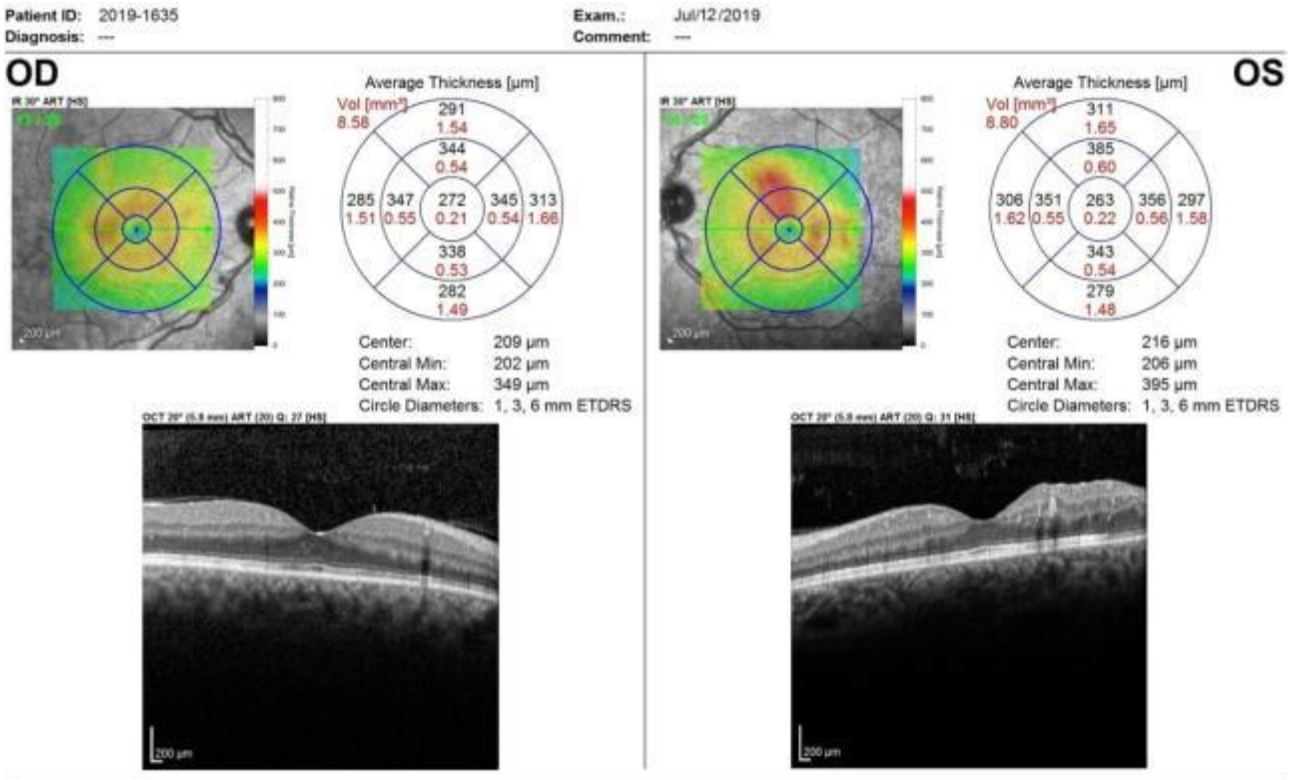

Figure (3): case no.1 (group 1) after injecting the left eye showing decrease CRT in both eyes and BCVA improved in left eye to 6/12 while remained 6/9 in right eye.

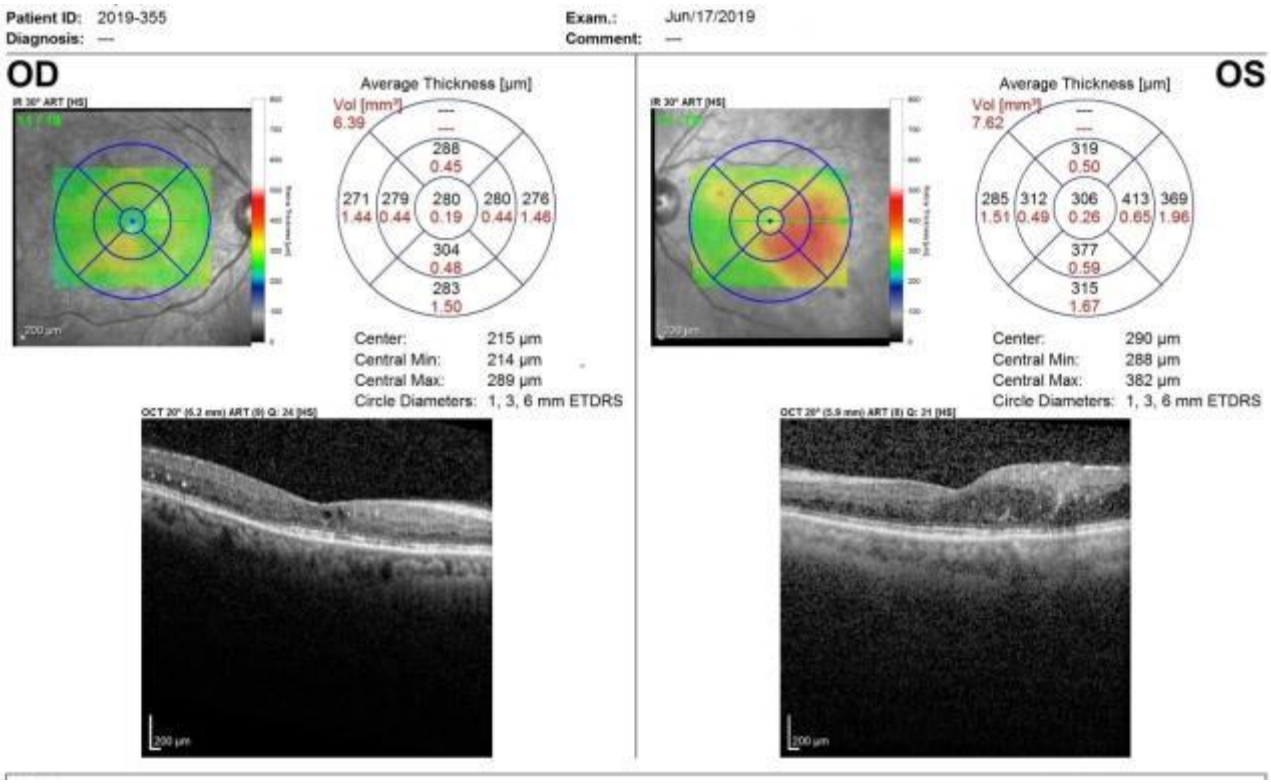

Figure (4): case no.10 (group 2) showing bilateral cystoid diabetic macular edema pre-injection, the BCVA was 6/9 and 6/12 by snellen chart for right and left eye respectively.

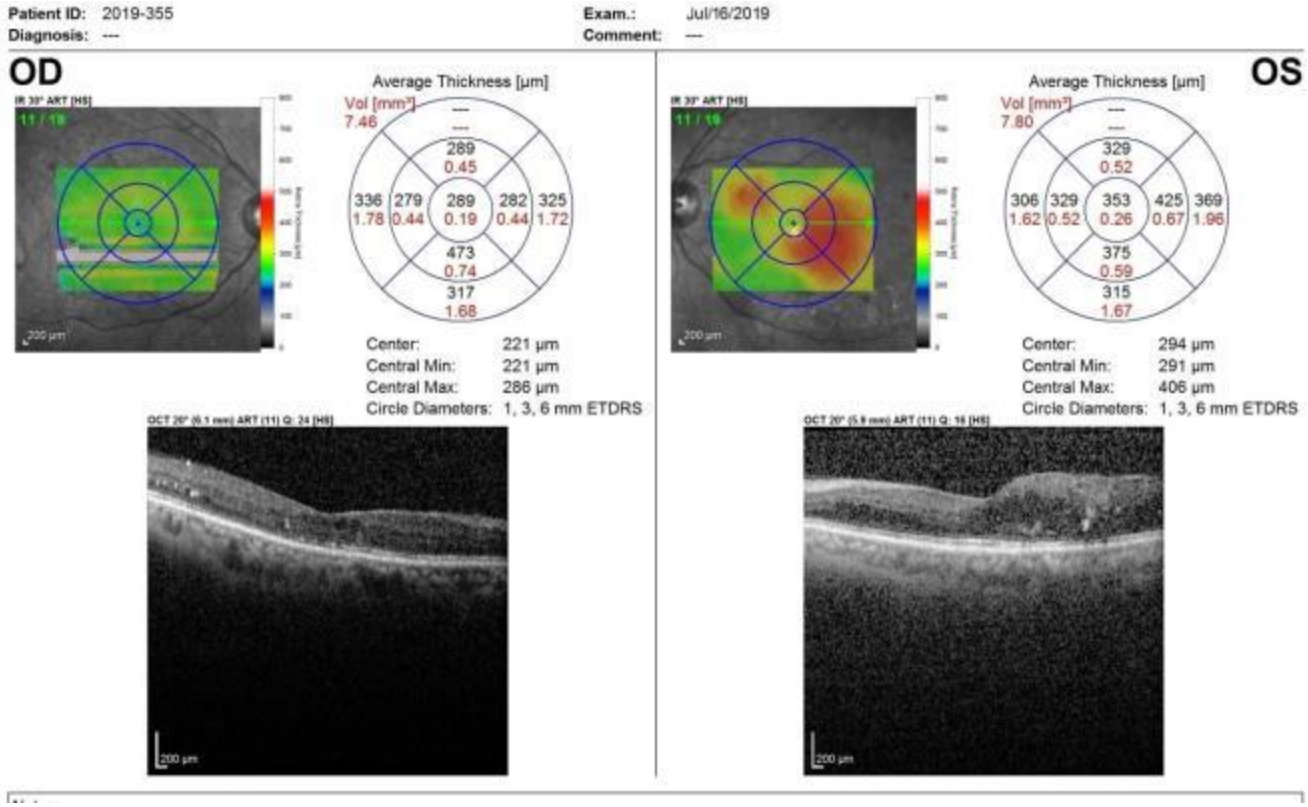

Figure (5): case no.10 (group 2) after injecting the left eye showing decrease CRT in the injected eye while the right eye (the fellow eye) showed increase in CRT but only 10 µm and BCVA remained unchanged in both eyes.

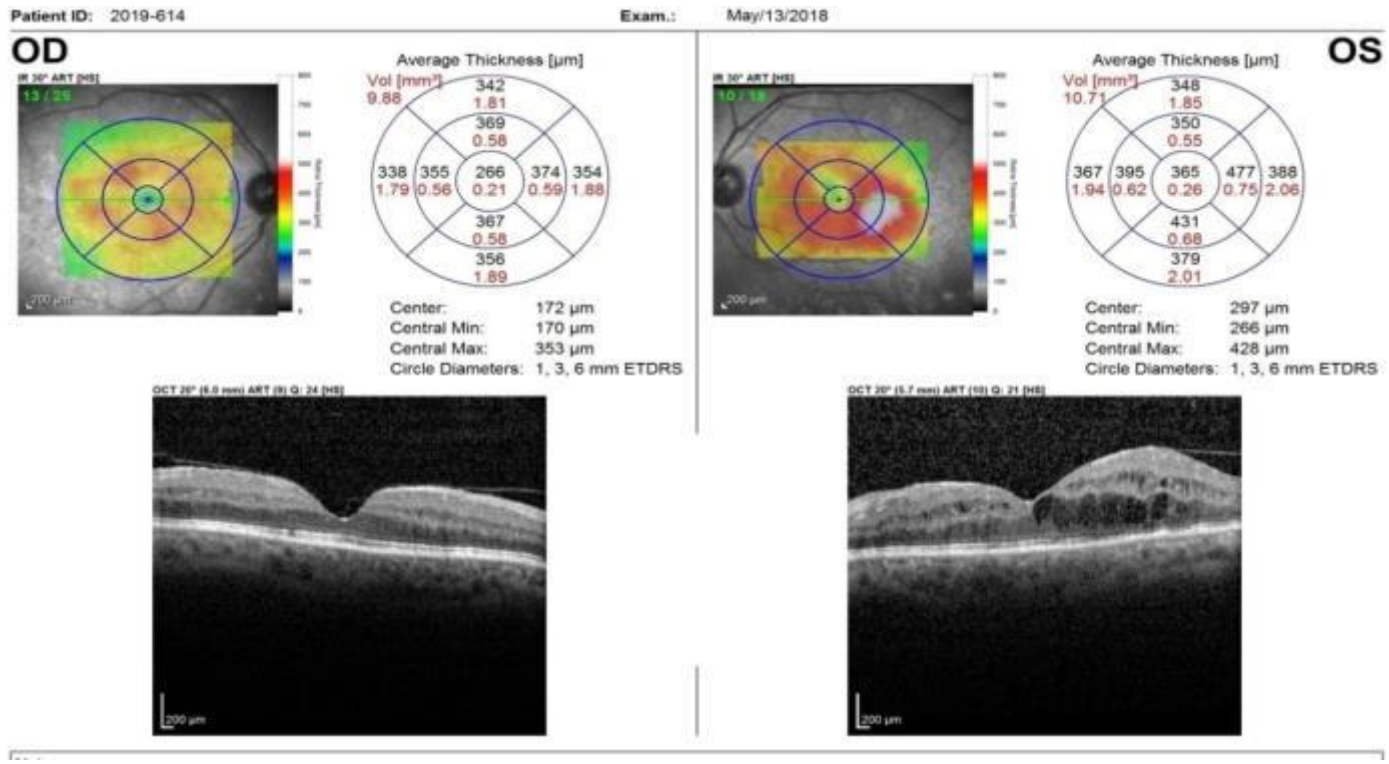

Figure (6): case no.19 (group 3) with positive albuminurea had right diffuse DME and left cystoid DME pre-injection. The BCVA 6/9 and 6/12 for the right and left eye respectively.

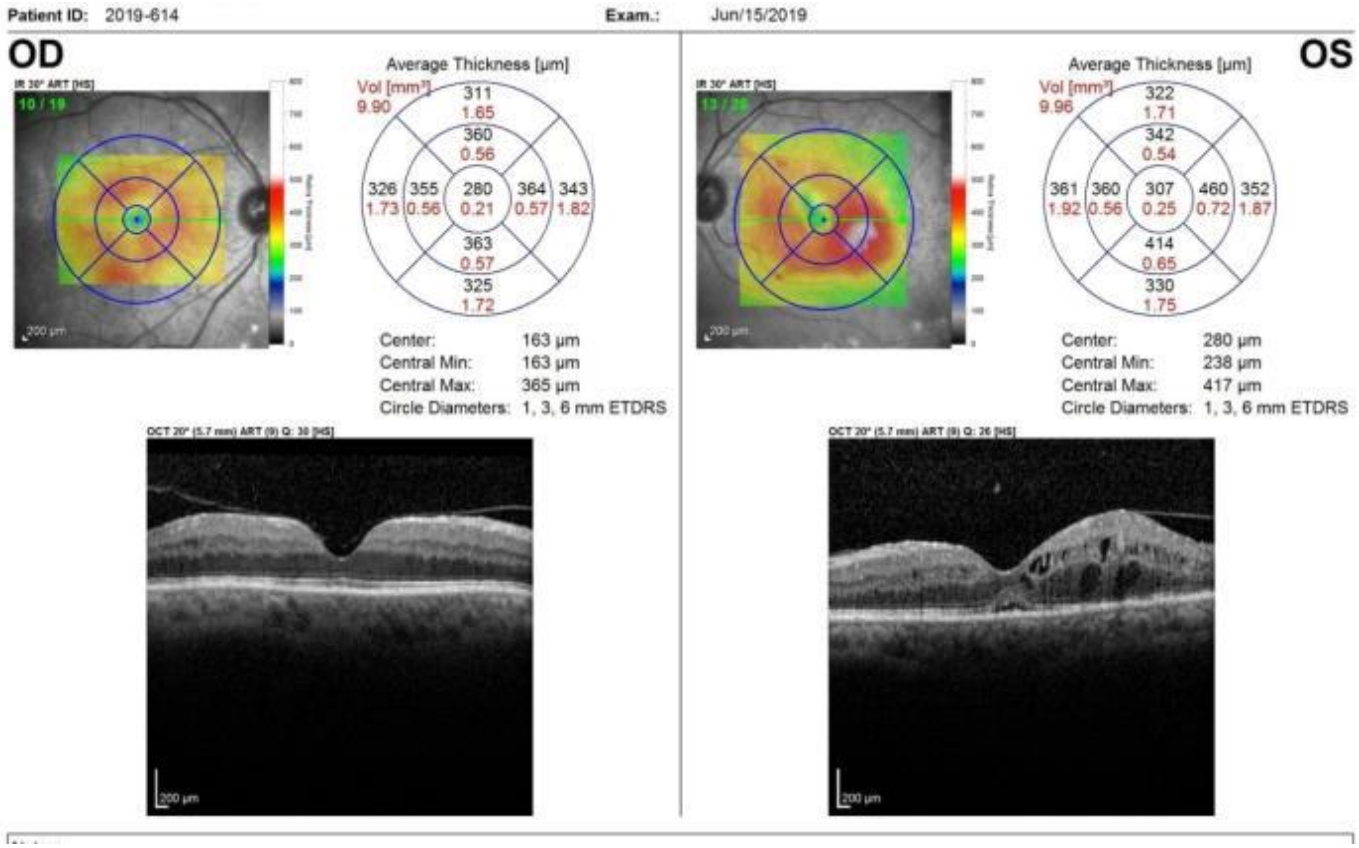

Figure (7): case no.19 (group 3) after injection of the left eye, showing improvement in CRT of left eye (injected eye) while the CRT of the right eye (untreated eye) increased. The BCVA of both eyes didn't Mean best corrected visual acuity (BCVA) by ((LogMAR) approximate snellen equivalent) significantly improved in injected eye but remain unchanged in the fellow eye as showed in table (6) and (7).

Table (6): The mean BCVA in the injected eye pre and post injection and it's significance.

		Mean ± SD	T	P value
Injected eye	**Pre-injection**	0.51 ± 0.215 (6/18)	29	0.0001
	Post-injection	0.33 ± 0.180 (6/12)		

Table (7): The mean BCVA in the fellow eye pre and post injection and it's significance.

		Mean ± SD	T	P value
fellow eye	**Pre-injection**	0.34 ± 0.229 (6/12)	29	0.476
	Post-injection	0.34 ± 0.239 (6/12)		

On examination there were no significant abnormalities in anterior segment, all the patients had normal color vision by ishihara plates. Amselar grid was normal in Twenty-six cases while four cases were distorted.

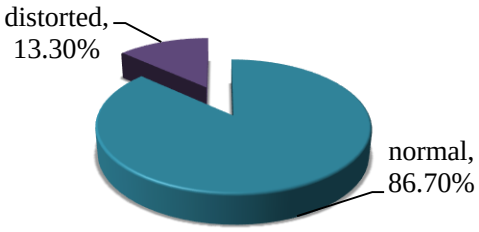

Figure (8): Amselar grid distribution among the patients.

70 % of cases were hypertensive (21 cases) and 30 % normotensive (9 cases) and 93.3 % of cases without albuminurea (28 cases) 6.7 % with albuminurea (2 cases) as showed in. There is no statistically significance correlation between hypertension and the change of CRT in both eyes. As showed in tables (8), (9), (10).

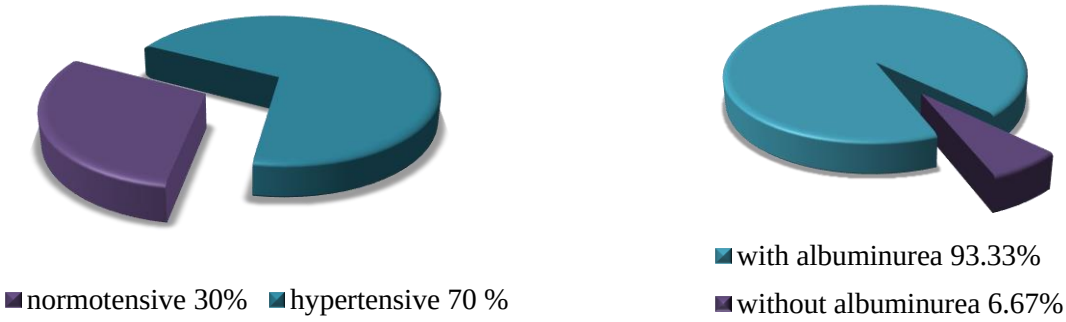

Figure (9): distribution of hypertension and albuminurea distribution in the study.

Table (8): Correlation between hypertension and reduction in CRT of Injected eyes and its significance:

	Mean±SD	T	P value
Hypertensive	88.14 ± 34.26	1.37	0.183
normotensive	71.22 ± 22.16		

Table (9): Correlation between hypertension and reduction in CRT of Fellow eyes and its significance:

	Mean ± SD	T	P value
Hypertensive	11.76 ± 14.8	0.298	0.768
normotensive	10.22 ± 6.3		

Table (10): The correlation between albuminurea and the change in the fellow eye:

	-ve albuminurea	+ve albuminurea	Total
Group 1	17	0	17
Group 2	10	0	10
Group 3	1	2	3

DISCUSSION

Anti-VEGF antibodies nowadays considered the first-line treatment in DME. Reaching Anti-VEGF drugs administered through intravitreal route in human's eyes the systemic circulation is a fact which has been widely accepted.

This is supported by few studies regarding the pharmacokinetics and distribution of these agents after intravitreal injection that demonstrating decrease in VEGF levels in the blood after intravitreal injections as **Sato *et al.*** [6] have found significant decrease in serum VEGF levels 1 week after injecting 0.5 mg IVB. **Carneiro *et al.*** [7] showed a 42% decrease in serum VEGF after a third IVB in patients with neovascular AMD. **Zehetner *et al.*** [8] also found similar effects after IVB,

Zehetner *et al.* [9] conducted another study on aflibercept which gave a similar effect on systemic VEGF level. Along with **Hoerster *et al.*** [10] who reported that serum VEGF levels in infants with ROP reduced after 2weeks from injection of 0.2mgofranibizumab.

Our study demonstrates the presence of statistically significant effect of a single 0.5mg ranibizumab injection on CRT of the contralateral but no significant improvement on BCVA. We selected patients with bilateral DME with no other ocular diseases and both eyes had didn't receive any treatment in the past. The worst eye diagnosed clinically through fundus examination and visual acuity and the CRT by OCT. They received a single injection and followed 4 weeks after by visual acuity and OCT.

- **Central macular thickness:**

According to CRT changes our results agreed with that of **Sharma and Ong *et al.*** [11], as they reported a case showed a significant improvement in macular thickness of the non-injected eye of a patient receiving unilateral ranibizumab for diabetic macular edema. **Rotsos *et al.*** [12], reported a case with bilateral DME who showed significant anatomical improvement and reduction in CRT was observed in the fellow eye after 2 intravitreal ranibizumab injections in one eye.

There are studies demonstrated that there is contralateral effect in DME but with others anti-VEGF agents as **Rahimy *et al.*** [13], reported a case with bilateral diffuse DME received single unilateral intravitreal aflibercept injection and showed bilateral response and improvement in CRT and **Bakbak *et al.*** [14] reported in patients with bilateral DME. A significant contralateral effect but after intravitreal bevacizumab injection in one eye

Other studies showed the contralateral effect of ranibizumab in other diseases as **Wu and Sadda** [15] reported a case with branch retinal vein occlusion (BRVO) in which ranibizumab appeared to have effects in the contralateral untreated eye. Another study conducted by **Acharya *et al.*** [16] demonstrated a beneficial effect of ranibizumab in both eyes of patients (2 out of 3 patients) who were treated with unilateral ranibizumab injection but for uveitis-related CME and **Pescosolido *et al.*** [17] who reported a case with bilateral subfoveal choroidal neovascularization, the case was injected with ranibizumab showed remission of the CNV of both eyes but after the second injection.

Our results not agreed with that of **Bakbak *et al.*** [14], who found statistically significant decrease in CRT in untreated eyes after treatment with bevacizumab, but not ranibizumab. Recently **Malbin *et al.*** [18] conducted a comparative study to see the contralateral effect of the three anti-VEGF agents, bevacizumab, ranibizumab and aflibercept, in patients with bilateral DME and found only aflibercept that reduced the CRT of the fellow eye significantly.

Also, there are studies demonstrated that ranibizumab had no effect on the fellow eye in other retinal diseases as **Gamulescu and Helbig** [19], who observed no therapeutic effect of ranibizumab in the untreated fellow in patients with ARMD.

While in the same year to see the effect of anti-VEGF agents on the fellow eye in patients with DME **Velez-Montoya *et al.*** [20] designed a study and found no significant change in CRT of the untreated eye 4 weeks after bevacizumab injection in one eye in patients with bilateral DME.

- **Visual acuity:**

Our results of the BCVA agreed with **Bakbak *et al.*** [14] as he evaluated a crossover effect of ranibizumab in patients with bilateral DME. He have found no statistically significant change on BCVA in the contralateral eye, in patients with DME. **Malbin *et al.*** [18] supported our results in his study that mentioned before and found the change between the initial visual acuity and 1-month after the injection in the 3 fellow-eye groups was not statistically significant.

And about the concept of the effect of anti-VEGF on the fellow eye we are in line with **Hanhart *et al.*** [21] as he evaluated the effect of bevacizumab in patients with bilateral DME and found there was no significant improvement of the VA in the non-injected eye.

On the other hand, our results did not agree with **Rotsos *et al.*** [12], who reported a significant visual improvement in the fellow eye after 2 ranibizumab injections in their case report.

But according to other retinal diseases **Rouvas *et al.*** [22] conducted a retrospective study in patients with ARMD and demonstrated visual improvement in contralateral eye after intravitreal

ranibizumab injection. And **Pescosolido *et al.* [17]** also reported a statistically significant improvement in BCVA untreated eye of the patient with CNV after the second ranibizumab injection.

It has been observed that the responses to anti-VEGF treatments are very variable among diabetic patients and unpredictable. **Kim *et al.* [23]** have found that the response to the treatment strategies may be affected by DME patterns determined by OCT.

So, it can be suggested that a good understanding of if the systemic risk factors may affect the morphology of the macula in DME so that would help predict treatment outcome.

Acan *et al.* [24], found that Micro-albuminurea or macro-albuminurea may be more frequent and HbA1c level may be higher in patients with Diffuse macular edema.

In our study we noticed that patients with albuminurea their CRT of the fellow eye increased post-injection and the injected eye's CRT improvement was less than patients without albuminurea. So, it can be suggested that the systemic condition of diabetic patients may affects their response to injection as the albuminurea is a major risk factor in development of DME.

But we didn't find any significance relation between hypertension and the improvement of the fellow eye. This may agree with **Chew [25]**, who discussed the results of the ACCORD Eye Study (Action to Control Cardiovascular Risk in Diabetes), a randomized controlled clinical trial that examined the benefits of intense blood glucose control, blood pressure, and serum lipid levels on retinopathy in type 2 diabetes patients.

And her clinical recommendations were that intensive glycemic control are important in the treatment of DR but Intensive blood pressure control (that the systolic to be below 140 mm Hg) may not be necessary because of the weak evidence of benefit from blood pressure control in the progression of DR **[2].**

The mechanism of effects of injection anti-VEGF agents on the contralateral eye is controversial till now. The molecule has been shown to pass into the eyes from the systemic circulation after systemic use of bevacizumab in patient with ARMD according to **Michels *et al.* [26]**.

To explain the effect in the untreated eye, **Pescosolido *et al.* [17]** hypothesized a neuronal or systemic diffusion of ranibizumab that is able to induce the same effects in the contralateral eye as in the treated eye. Ranibizumab is smaller in molecular weight in comparison with bevacizumab, so it is possible that it may reach the contralateral eye more easily through the systemic circulation.

However, animal studies have shown that while both bevacizumab and ranibizumab were found in small amounts in the serum of rabbits after intravitrealadministration, only bevacizumab reached and was found in the aqueous of the fellow eye **Acharya *et al.* [16]**.

We are not sure about why we found a fellow eye effect in our patients treated with unilateral ranibizumab. Our theory is that the control of systemic risk factors such as HbA1c and hypertension along with kidney functions is the main reason this theory supported by our results about the patients with albuminuria whom their CRT increased after the injection.

If we took serum assays and vitreous or aqueous samples before and after intravitreal injection, we would have a better idea about the pharmacokinetics of ranibizumab. However, at the time of designing this study, we believed that these were invasive procedures for our study, which was aimed at identifying changes in BCVA and CRT

And about the lack of BCVA effect we believed that because we only administered single injection as it has been suggested that the altered blood-retina barrier resulted from diabetes may require multiple doses of anti-VEGF injections before maximal clinical response can be seen in DME

However, our results support the hypothesis that ranibizumab treatment in one eye may have a contralateral effect and this will have a lot of benefits to the patients and decrease the cost.

The short follow-up time, small sample size, and the absence of a control group of untreated patients are the major limitations in our study. Along with the shortage in similar literatures that focus on the potential therapeutic effect of intravitreal ranibizumab in the fellow eye in patients with bilateral DME as most of literatures focused mainly on exudative AMD and the bevacizumab agent.

CONCLUSION

It could be concluded that ranibizumab can escape into the systemic circulation and reduce contralateral CRT and the systemic condition could affect the outcome of the treatment.

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