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Safety of intravitreal anti-VEGF injections in diabetic macular edema

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Short title: Safety of intravitreal anti VEGF injections in DME.

Abstract

Propose: Diabetic macular edema (DME) is the most common cause of visual impairment in patients with diabetes mellitus. The pathogenesis of DME is complex and multifactorial. DME can be diagnosed using noncontact stereoscopic biomicroscopy, contact lens biomicroscopy, Fundus fluorescein angiography (FFA), and Optical Coherence Tomography (OCT). Intravitreal anti-vascular endothelial growth factor (VEGF) agents have been investigated in the treatment of DME. This study aims to investigate the safety of intravitreal anti-VEGF during a six-month follow-up.

Methods: Sixty patients with type I or II diabetes mellitus complaining from central involved DME were recruited for this longitudinal study. All patients were subjected to full history taking, complete ophthalmological examination, systemic evaluation, FFA, and OCT imaging. Patients were subdivided into three groups, 20 patients each: Ranibizumab group, Bevacizumab group, and Aflibercept group.

Results: After 6-month follow-up, the ranibizumab group showed slightly higher systemic cardiovascular and cerebrovascular accidents rates, while the Bevacizumab group showed insignificant higher risk of ocular inflammation and endophthalmitis, aflibercept has the least incidence of ocular adverse effects.

Conclusion: Anti-VEGF intravitreal injections are relatively safe for the treatment of DME. Aflibercept showed the least incidence of ocular side effects. The current study suggested that intravitreal anti-VEGF could be administered safely to diabetic patients with decreased glomerular filtration rate (GFR).

Keywords: aflibercept, ranibizumab, bevacizumab, Diabetic Macular Edema, Muller cells, vascular endothelial growth factor (VEGF).

INTRODUCTION:

About a third of diabetic people have diabetic retinopathy (DR), and about a tenth are affected by Diabetic Macular Edema (DME). The incidence of DME increases with diabetes duration, hemoglobin A1C, and blood pressure levels, it is higher in people with type 1 compared with type 2 diabetes[1].

Macular edema is defined as the accumulation of excess fluid in the extracellular space of the neurosensory retina causing abnormal thickening of the macula. Intracellular fluid involving Muller cells can be observed in some histopathological cases[2].

Diabetic Macular Edema results from retinal microvascular changes. Thickening of the basement membrane and reduction in the number of pericytes are believed to increase permeability and incompetence of the retinal vasculature. Leakage of plasma constituents to the surrounding retina, with subsequent retinal edema due to compromised blood-retinal barrier (BRB). Hypoxia produced by this mechanism can also stimulate the production of vascular endothelial growth factor (VEGF). There is evidence

that VEGF is up-regulated in DME and proliferative diabetic retinopathy[3].

A great variety of morphological patterns became apparent, even though all patients had the same underlying disease[4]. So, a combination of Optical Coherence Tomography (OCT) with Fundus Fluorescein Angiography (FFA) is considered more advantageous for the classification of DR.

Morphological biomarkers - recognized on OCT or FFA - can define patients with recalcitrant disease; and thus, help to guide and predict the prognosis of individual treatment regiments[5].

Although the standard treatment of DME is focal laser photocoagulation, it can only slow progression with a low ability to reverse vision loss[6]. Antiangiogenic therapy has largely replaced laser photocoagulation as it was proven to be more effective[7].

Recently, anti-VEGF therapy is considered the primary treatment for DME involving the center of vision, while macular focal/modified grid lasers still have a role in clinically progressive non-center involving DME[8]. A recent clinical trial suggests that a combination of intravitreal Bevacizumab and focal macular photocoagulation had higher efficacy than Bevacizumab alone[9].

Anti-VEGF agents, interrupting a critical stimulus for the development of BRB breakdown, have been studied in the treatment of DME, such as Pegaptanib sodium (Macugen, Eyetech Pfizer), Ranibizumab (Lucentis, Genentech Inc., San Francisco, CA), Bevacizumab (Avastin, Genentech, and South San Francisco, CA) and aflibercept (Eylea, Regeneron, NY, USA) .

Although bevacizumab is currently approved by FDA (Food and Drug Administration) for the treatment of metastatic colorectal cancer, it is widely off-label used in treatment for neovascular age-related macular degeneration (ARMD) and retinal vascular disorders including retinal vein occlusion and DME due to its low cost[10].

The diabetic retinopathy clinical research network trial (DRCR.net) evaluated the short-term value of intravitreal bevacizumab in diabetic patients demonstrating a beneficial effect in center-involved DME[11].

Treatment effectiveness indicators include duration of diabetes, number of injections, and response to previous treatments in conjunction with visual acuity, central macular thickness (CMT), and residual macular edema presenting within or under the retina .

Compared to intravenous anti-VEGFs, used for cancer treatment, the much lower dose of intravitreal anti-VEGFs had fewer systemic adverse effects. These adverse effects, however, increase in high-risk patients with intense anti-VEGF treatment for two years[12]. Although the intravitreal route is associated with less systemic adverse effects, it is associated with ocular adverse effects: including infectious endophthalmitis, post-injection inflammation, and post-injection increase in intraocular pressure[13].

This study aims to evaluate systemic and ocular adverse effects of intravitreal anti-VEGF during a six-month follow-up.

PATIENTS AND METHODS

This prospective interventional randomized study was held on 60 eyes of 60 patients at the Retina Clinic of Mansoura University ophthalmology center from October 2018 to October 2019. The study was pre-approved by the ethical committee at Mansoura University in 2017. Approval code: MD/17.01.41

The study included patients above the age of 18 diagnosed with type 1 or 2 DM who had center involved DME with the following criteria:1- Clear media enough to document macular edema by OCT. 2- Definite retinal thickening due to DME involving the center of macula > 300 µm by OCT, assessed to be the main cause of visual loss. 3- Best corrected visual acuity less than .2 log MAR.

Exclusion Criteria: 1- Associated vitreoretinal changes: subretinal fibrosis, significant vitreoretinal traction on OCT indicating vitrectomy or poor prognostic factors for injection like distorted inner retinal layers, disrupted ellipsoid zone, or macular ischemia. 2- Patients treated with laser or intravitreal injection in the last six months. 3- Associated ocular diseases such as glaucoma, glaucoma suspect, ocular hypertension, or significant cataract which affects vision. 4- Systemic diseases that interfere with Anti VEGF injections such as Recent stroke or transient ischemic attack. 5- Ocular surgery: like a glaucoma-related procedure.

The patients were classified randomly into three groups: Group A (20 patients): received Lucentis (Ranibizumab .5mg) 3 injections, a month apart. Group B (20 patients): received Avastin (Bevacizumab 1.25 mg) 3 injections, a month apart. Group C (20 patients): received Eylea (Aflibercept 2 mg) 3 injections, a month apart. After the third injection, we followed the patients for any further improvement or worsening until 6 months. Starting from the third month, injections were resumed in recurrent cases according to the following criteria:

1. Loss of BCVA ≥ 1 line after treatment (functional recurrence).
2. Recurrence or persistence of ME as documented by indirect fundus ophthalmoscopy and spectral-domain OCT (Anatomical recurrence).

A simple random sample was done using randomly picked, concealed numbers; each number corresponding to one treatment group. All patients provided informed written consent before baseline assessment.

Statistical analysis was done using IBM's SPSS statistics (Statistical Package for the Social Sciences) for windows (version 25, 2017). Quantitative variables such as mean and standard deviation, median, interquartile range, minimum, and maximum as appropriate were expressed. Categorical variables were expressed as frequency and percentage.

Inter-group comparison of parametric and non-parametric continuous data with no follow-up readings was done using One-way ANOVA with Bonferroni post hoc analysis and Kruskal Wallis with Dunn's post hoc analysis tests respectively.

For pair-wise comparison of data (within subjects), the follow-up values were compared to their corresponding basal value using paired samples T test or Wilcoxon matched pairs signed ranks test.

Inter-group comparison of nominal data with the crosstabs function was done using Fisher exact and Chi-square tests. The normality of data distribution was checked using the Shapiro-Wilk test. All tests were conducted with a 95% confidence interval. Statistical significance was considered if ($P < .05$).

RESULTS:

Sixty eyes of sixty patients with type 1 or 2 diabetes were involved in this study. The mean age of the patients was 61.62 with SD 8.33 (range 18-75years), there were 37 male (61.7 %) and 23 female (38.3 %) subjects. Patients were randomized into three groups, 20 eyes (20 patients) were treated with intravitreal Bevacizumab 1.25 mg (IVB group), 20 eyes (20 patients) received intravitreal Ranibizumab .5mg (IVR group) and 20 eyes (20 patients) treated with intravitreal Aflibercept 2 mg (IVA group).

Among the Bevacizumab group, ten patients were males, and ten patients were females with a mean age of 59.05 years. The duration of diabetes was an average of 12.55 years. Among the Ranibizumab group, there were 12 male patients and 8 female patients; and the mean age was 62 years. The duration of diabetes was an average of 11.90 years, while in the Aflibercept group there were 15 males and 5 females with an average age of 63.8 years and disease duration of 12.10 years. HbA1c % (7.30, 7.70, 7.45), IOP mmHg (17.8, 17.55, 17.62), Phakic eyes % (80, 90, 70), Pseudophakic eyes % (20, 10, 30) in three groups (Table 1).

Table 1: Baseline demographic analysis between the treatment groups

		Bevacizumab	**Ranibizumab**	**Aflibercept**	***P***
Age		59.05 ± 10.49	62.00 ± 6.52	63.80 ± 7.18	.192
Gender	Male	50.0% (10)	60.0% (12)	75.0% (15)	.262
	Female	50.0% (10)	40.0% (8)	25.0% (5)	
Duration of DM		12.55 ± 3.03	11.90 ± 3.09	12.10 ± 4.46	.842
HbA1c		7.30 ± 0.92	7.70 ± 1.17	7.45 ± 1.19	.515
IOP		17.87 ± 0.746	17.55 ± 0.726	17.62 ± 0.57	.307
Lens state	Phakic	80.0% (16)	90.0% (18)	70.0% (14)	.346
	PCIOL	20.0% (4)	10.0% (2)	30.0% (6)	

Data are expressed as mean and standard deviation or percentage and frequency. P is significant when ($P < .05$).

IOP: Intraocular pressure, PCIOL: Posterior chamber intraocular lens.

Injection-related infectious endophthalmitis occurred in two bevacizumab-treated eyes and no ranibizumab-treated or aflibercept-treated eyes.

Ocular inflammation other than endophthalmitis was reported in one ranibizumab-treated eye, three bevacizumab-treated eyes, and two aflibercept-treated eyes. Ocular adverse events are detailed in Table 2.

Table 2: Ocular adverse effects during the follow-up period in the studied groups

	Bevacizumab	**Ranibizumab**	**Aflibercept**	***P***
Endophthalmitis	10% (2)	0% (0)	0% (0)	.322
Inflammation	15% (3)	5% (1)	10% (2)	.863
Retinal detachment	0% (0)	0% (0)	0% (0)	-
Vitreous haemorrhage	5% (1)	5% (1)	0% (0)	1
Cataract	5% (1)	0% (0)	0% (0)	1

Data are expressed as percentage and frequency. P is significant when ($P < .05$).

Mean IOP values changed from 17.69 ± 0.69 at baseline; to 21.96 ± 1.53 after one hour, 19.62 ± 1.53 after one week, and 18.5 ± 1.41 after one month. We excluded glaucoma, glaucoma suspect, and ocular hypertension cases from our study.

No significant differences were found in IOP elevations between the three groups depending on the anti-VEGF agent used (bevacizumab, ranibizumab, or aflibercept) as shown in table 3, although the bevacizumab group seemed to induce a slightly higher IOP level than other two groups. (Fig. 1)

Table 3: Basal and follow-up mean IOP values in the studied groups

IOP	**IVB**	**IVR**	**IVA**	***P***
Basal	17.88 ± 0.75	17.56 ± 0.77	17.63 ± 0.57	.307
One hour	21.91 ± 1.5	21.41 ± 1.84	21.75 ± 1.24	.580
One week	19.83 ± 1.54	19.37 ± 1.8	19.64 ± 1.23	.640
One month	18.68 ± 1.33	18.30 ± 1.72	18.52 ± 1.17	.708

Data are expressed as mean and standard deviation. P is significant when ($P < .05$)

IOP: intraocular pressure, IVB: Intravitreal bevacizumab. IVA: Intravitreal aflibercept. IVR: Intravitreal ranibizumab.

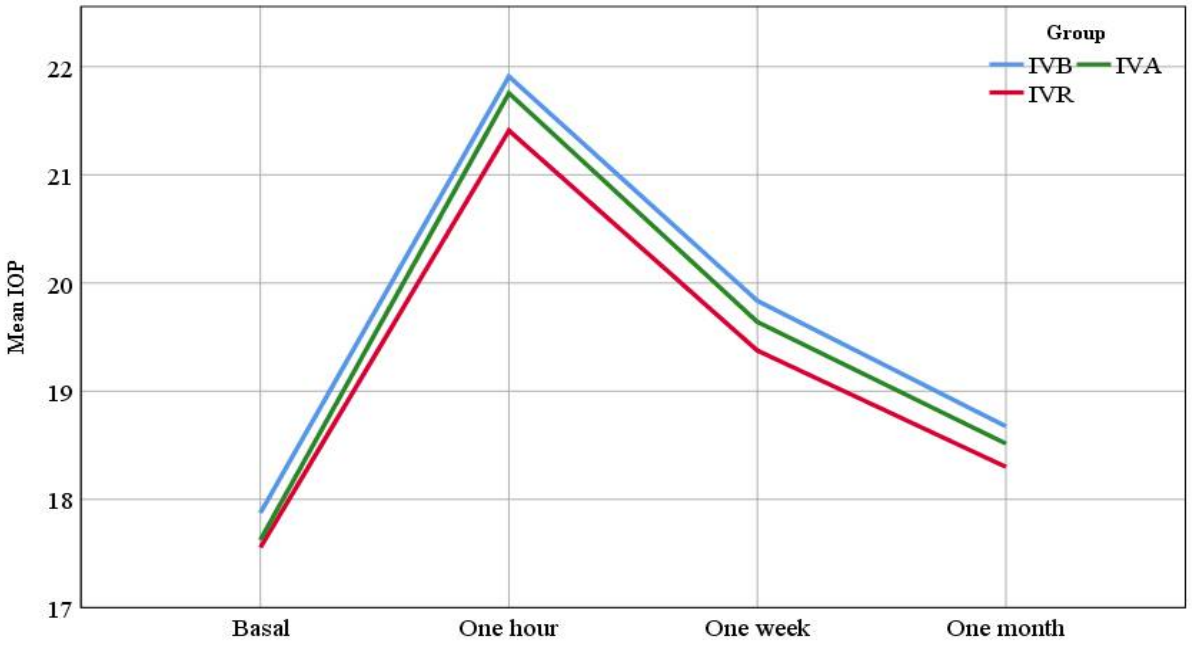


Fig. 1: Variation of mean IOP values after the intravitreal injection in the studied groups. IVB: Bevacizumab, IVA: Aflibercept, Ranibizumab.

The rate of systemic adverse events was mostly similar in the three treatment groups. The present rate of cardiovascular and cerebrovascular events was more evident in the ranibizumab group than in the other two groups, with a non-significant P value. The current study tried to detect the effect of intravitreal anti-VEGFs injection in DME on renal functions, by measurement of estimated GFR before and after intravitreal injections. Overall, no significant changes in estimated GFR were observed after the three injections in three groups (86 ± 15, 83 ± 12, and 85 ± 17 respectively; (P = .768), when compared with before the injections (91 ± 16, 88 ± 12, and 90 ± 16 respectively; (P = .784). Systemic adverse events are detailed in Table 4.

Table 4: Systemic adverse effects during the follow-up period in the studied groups

		Bevacizumab	Ranibizumab	Aflibercept	P
cardio & cerebrovascular events		5% (1)	15% (3)	10% (2)	.56
Estimated GFR	Pre-injection	91.68 ± 16.48	88.40 ± 12.16	90.77 ± 16.88	.784
	Post-injection	86.68 ± 15.99	83.07 ± 12.98	85.10 ± 17.89	.768

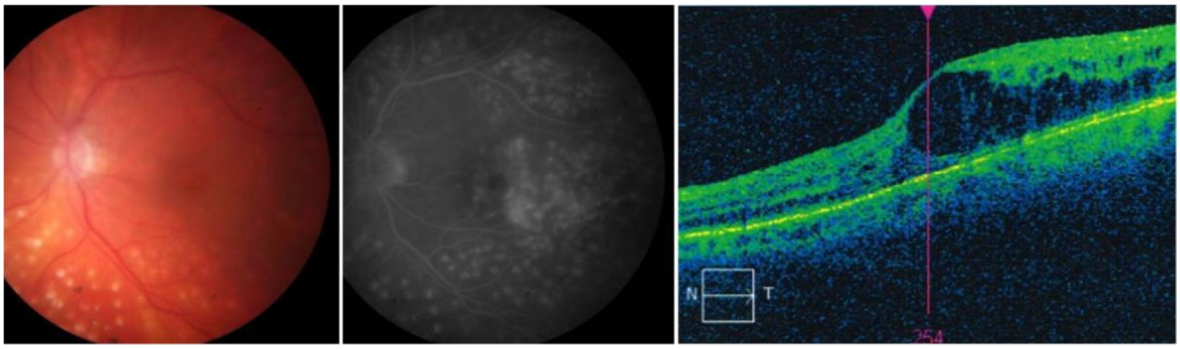
Data are expressed as percentage and frequency. P is significant when < 0.05.

GFR: glomerular filtration rate.

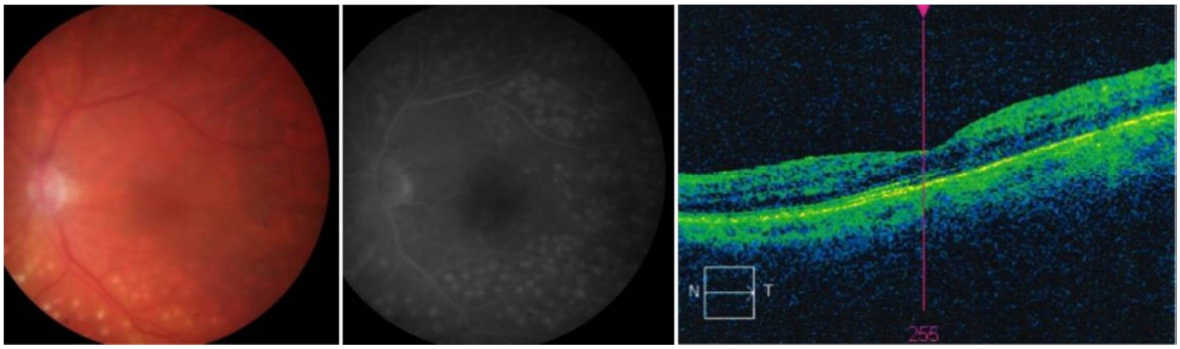
Figure (2) shows the left eye of a 50-year-old male patient, diabetic for 20 years, not hypertensive. At baseline, FFA revealed a massive leakage (hyper-fluorescence) of dye in the macula, corresponding DME involving center present on OCT scan also there was distorted IS / OS complex.

After 3 months of treatment by ranibizumab, the absence of dye leakage in macular region was obvious in FFA and OCT scan showed a reduction in macular thickness and less distorted IS / OS complex.

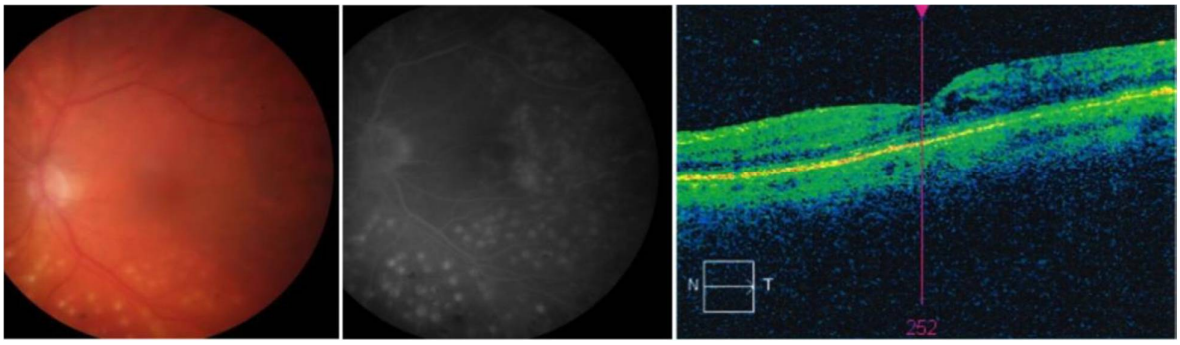
After 6 months of follow-up, an increase in dye leakage in FFA was apparent; corresponding to small intraretinal fluid and increased macular thickness up to 280 µm in OCT. However, no significant change in BCVA was detected. (Fig. 2)



A: Baseline: BCVA: 0.44 log MAR



B: 3rd month: BCVA: 0.2 log MAR



C: 6th month: BCVA: 0.24 log MAR

(Fig. 2): A: pre-injection, B: month 3, C: month 6

DISCUSSION:

Diabetic Macular Edema is a chronic disease with variable responses and clinical manifestations during the whole life of the affected patients. Therefore, a single treatment may not be enough for the entire course of the disease[14].

A comprehensive approach should include the complex pathogenetic mechanism underlying DME and match it with any specific manifestation[15].

Therefore, there is no 100% successful treatment for DME, and recurrence is the rule in the majority of cases treated with one or more of the currently available treatment modalities[16,17].

The commonest Anti-VEGF agents used in DME are aflibercept, bevacizumab, or ranibizumab. The three agents differ in structure, growth factor specificity, and VEGF-binding affinity; but the ways these differences may relate to efficacy are not fully known[18].

Bevacizumab is by far the most used anti-VEGF agent globally, it is important to inform clinicians, patients, and funders that bevacizumab and ranibizumab are similar for treating DME based on published trials comparing the 2 drugs in age-related macular degeneration[19].

Recurrence of macular edema with bevacizumab injection was observed within a few weeks after the treatment, and so repetition of Bevacizumab was considered by many surgeons[20,21].

Many studies evaluated the treatment response behavior of aflibercept in DME like the DA VINCI study, which differs in design from the more recent VIVID-DME and VISTA-DME studies in many aspects, including loading phase (DA VINCI included three initial loading doses in some arms compared with five in VIVID-DME and VISTA-DME).

This current study tried to highlight the safety of intravitreal bevacizumab, ranibizumab, or aflibercept injection in treating central-involved DME.

To know the difference in study design, VISTA and VIVID trials demonstrated substantial improvements in BCVA and CST among eyes treated with aflibercept regardless of whether the eyes had previously been treated with anti-VEGF 3 or more months before study enrolment. In this current study, we excluded cases of previous treatment.

This current study evaluated ocular and systemic adverse event outcomes of intravitreal aflibercept, ranibizumab, and bevacizumab in patients with DME. This study showed no significant differences between drugs in rates of ocular adverse events.

As regards endophthalmitis incidence, no significant difference was observed among the three groups in intraocular inflammation (P = .322 between groups), suggesting that there was adequate adherence to the aseptic injection procedure.

This agreed with DRCR.net Protocol T which reported that endophthalmitis only occurred in a single patient during the 24-month trial (0.5% of bevacizumab group; P = .66 between groups).

Although preoperative prophylactic topical antibiotic eye drops were used to lower endophthalmitis rates after IVI procedures, two cases in the bevacizumab group showed postoperative endophthalmitis. Torres-Costa S et al., 2020 reported no effect of antibiotic prophylaxis on the incidence of endophthalmitis[22].

As regards the results for the bevacizumab group, we referred them to repackaging the agent into single-use vials that underwent independent testing for sterility, purity, and potency before use. This standard may not always be feasible in clinical practice.

The present study removed all individuals previously diagnosed with glaucoma, glaucoma suspect, or ocular hypertension - as well as those who have taken glaucoma medication or underwent a glaucoma-related procedure.

Despite the removal of these high-risk patients, we still found an elevated risk of increased IOP in patients receiving anti-VEGF injections one hour after the procedure. IOP values varied from 1 hour, 1 week, and 1 month after treatment.

The type of injected drug (bevacizumab, ranibizumab, or aflibercept) did not have a statistically remarkable influence on the difference in IOP, but a slightly higher IOP was found in eyes receiving bevacizumab.

Mean IOP values reached 21.69 mm Hg 1 hour after injection in three groups, and after one week mean IOP decreased to 19.62 mm Hg. However, only four cases showed maintenance of IOP at levels higher than 21 mm Hg and needed topical medication to be controlled.

Lemos V et al., 2015 reported that 89% of patients receiving intravitreal ranibizumab experienced an IOP rise of more than 30 mmHg 5 seconds after injection, and approximately one third after the first 5 min[23].

The reason for the sustained increase in IOP is not completely understood and seems to be multifactorial. Yannuzzi NA et al., 2014 speculated that using higher injection volumes as well as a rapid injection technique may both lead to sustained IOP elevation[24]. Kiddee W et al., 2015 suggested that Anti-VEGF agents may directly damage the trabecular meshwork[25].

Reis GM et al., 2017 attributed the sustained elevation of IOP to the passage of high molecular weight molecules through the anterior hyaloid or zonule, and consequent obstruction or damage of the trabecular mesh with repeated applications[26].

Meta-analyses of clinical trials involving the safety of ranibizumab showed that ranibizumab use for the treatment of DME had a minor risk for thromboembolic events compared with laser, triamcinolone acetate, or sham injection[27].

This current study showed that systemic cardiovascular and cerebrovascular accident rates were slightly higher in the ranibizumab group than in the other two groups, but with an

insignificant P value. Systemic risk factors such as the age of onset of diabetes, HbA1c, and gender contribute differently to the development of PDR and DME. In our study, there was no big difference between the three groups regarding these items[28].

DRCR.net, 2015 reported that the arm treated with intravitreal ranibizumab had significantly higher rates of arterial thrombotic events (5.4% aflibercept vs 7.8% bevacizumab vs 11.9% ranibizumab); a post hoc analysis explained that the statistical relation between ranibizumab and cardiovascular events might be due to chance. This study shows that the incidence of arterial thrombotic events was 10% aflibercept vs 5% bevacizumab vs 15% ranibizumab[29].

Wells JA, 2016 demonstrated that the rate of arterial thromboembolic events (ATE) in aflibercept, bevacizumab, and ranibizumab groups was 3%, 4%, and 5% respectively, this present study showed that the rate of cardiovascular and cerebrovascular events was 10%, 5%, and 15% respectively[30].

Analysis of previous studies involving persons with ARMD showed that aflibercept might be associated with a greater risk of stroke than ranibizumab among old persons (85 years or above).

On the other hand, a meta-analysis of the RISE, RIDE, VISTA, and VIVID trials reported an association between monthly ranibizumab and aflibercept over 2 years with an increased risk of cerebrovascular accidents, vascular deaths, but did not find a difference between ranibizumab and aflibercept[31].

Zarbin MA et al., 2017 found no meaningful differences between patients treated with 0.3 mg or 0.5 mg intravitreal ranibizumab versus control regarding the risk of stroke or TIA[32].

In this current study, we found no significant association between monthly ranibizumab, aflibercept, or bevacizumab with an increased risk of cardiovascular and cerebrovascular events over 6 months.

Several studies evaluating the safety and efficacy of anti-VEGF in diabetic patients had reported renal adverse effects, although the mechanisms are still debated[33]. A study was conducted on 121 patients to measure the effect of intravitreal bevacizumab on DME and noticed that only three cases had worsened kidney function[34].

Jamrozy-Witkowska A. et al., 2011 reported 1 diabetic patient with renal insufficiency after intravitreal Anti-VEGF (Bevacizumab) administration[35].

On the other side Kameda Y et al., 2018 evaluated renal safety following acute anti-VEGF exposure showing no significant change in mean estimated GFR and no episodes of acute kidney injury, following a single intravitreal anti-VEGF injection of ranibizumab, aflibercept, or bevacizumab[36].

After three intravitreal injections, there was no significant difference between the pre and post-injection values of estimated GFR in the study groups (ranibizumab, aflibercept, or bevacizumab). This suggests that intravitreal anti-VEGFs do not affect renal function, even in patients with diabetes and pre-existing reduced GFR - at least in short-term follow-up. The DRCR.net Protocol T trial reported that kidney dysfunction was high, but no differences were detected between groups after intravitreal injection of anti-VEGF.

limitations of this study: 1- The moderate sample size of 60 eyes limits the strength of the analysis. 2- Firm conclusion on the systemic safety of intravitreal anti-VEGF is limited as we measured GFR within just 30 days after administration. Therefore, we did not follow any longitudinal changes in renal dysfunction. 3- Patients with a recent stroke or transient ischemic attack were excluded from this study. Thus, the safety results of this study should be interpreted relative to this exclusion. 4- The 6-month follow-up is not enough to assess recurrence.

CONCLUSION:

Intravitreal aflibercept, bevacizumab, and ranibizumab were relatively safe treatments for DME with vision impairment. The safety profile of ranibizumab, aflibercept, and bevacizumab observed in this study was consistent with the well-established safety profile. The results of the present study show that aflibercept has a lower incidence of ocular adverse effects through a 6-months follow-up period.

DATA AVAILABILITY

All data are included in this article.

ACKNOWLEDGEMENT

None.

Conflict of Interest

Authors declare no conflicts of interest.

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Ethics declarations

Conflict of interest

Hossam Abouelkheir, Mohamed A. ELShafie, Maha M. Shahin, Mohamed M. Elwan, Rasheed S. EL-Lakkany, Hussen S. El-Ansarey, Rania K. Farag. all authors have no conflicts of interest that are directly relevant to the content of this review.

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