

## Evaluation of Intravitreal Aflibercept Injection for Macular Edema Secondary to Retinal Vein Occlusion

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### ABSTRACT

**Background:** To evaluate the efficacy of intravitreal aflibercept injection in eyes with macular edema due to retinal vein occlusion (RVO). **Patients and Methods:** prospective, non-randomized clinical study included 60 eyes of 60 patients with macular edema due to RVO. Thirty patients had branch RVO (BRVO) and 30 had central RVO (CRVO). Each patient had received intravitreal injection of aflibercept once followed by re-evaluation of BCVA and CMT monthly during the follow up period up to 6 months after injection. **Results:** One month after IV aflibercept injection in patients with RVO  $\leq 3$  months, the main best-corrected visual acuity improved from  $1.05 \pm 0.004 \mu\text{m}$  at baseline to  $0.75 \pm 0.07 \log\text{MAR}$  at 1 month, to  $0.58 \pm 0.10 \log\text{MAR}$  at 3<sup>rd</sup> month and at the 6<sup>th</sup> month improved to  $0.45 \pm 0.14 \log\text{MAR}$  ( $p \leq 0.05$ ). On the other hand, the mean BCVA improved from  $1.40 \pm 0.03 \mu\text{m}$  at baseline to  $1.13 \pm 0.07 \log\text{MAR}$  at 1 month, to  $0.98 \pm 0.06 \log\text{MAR}$  at 3<sup>rd</sup> month and to  $0.92 \pm 0.08 \log\text{MAR}$  at 6<sup>th</sup> month ( $P \leq 0.05$ ) in patients with RVO  $> 3$  months. The mean central macular thickness reduced from  $485.57 \pm 71.51 \mu\text{m}$  at baseline to  $316.78 \pm 58.38 \mu\text{m}$  ( $P \leq 0.05$ ) after 1 month, to  $259.45 \pm 50.84 \mu\text{m}$  ( $P \leq 0.05$ ) at the 3<sup>rd</sup> month and to  $225.85 \pm 34.44 \mu\text{m}$  ( $P \leq 0.05$ ) at 6<sup>th</sup> month in patients with RVO  $\leq 3$  months. Meanwhile, in those with RVO  $> 3$  months the main CMT reduced from baseline  $625.91 \pm 167.56 \mu\text{m}$  to  $395.07 \pm 98.89 \mu\text{m}$  ( $P \leq 0.05$ ), to  $319.53 \pm 53.28 \mu\text{m}$  ( $P \leq 0.05$ ) and at the 6<sup>th</sup> month reduced to  $276.50 \pm 38.89 \mu\text{m}$  ( $p \leq 0.05$ ). No intra-operative or post-operative complications as retinal detachment, vitreous hemorrhage, or elevated intraocular pressure. Subconjunctival hemorrhage or local hyperemia at the injection site may be observed in some cases. Long term duration without treatment is associated with less improvement in the visual acuity. **Conclusion:** Intravitreal injection of aflibercept is more clinically effective and generally well tolerated for treatment of macular edema due to RVO.

**Key words:** Aflibercept, RVO, ME.

### INTRODUCTION

Retinal vein occlusion (RVO) is a common sight-threatening vascular disorder of the retina, in which macular edema is the main cause of visual impairment [1]. It may involve the central (CRVO) or a branch (BRVO) retinal vein, which may be caused by a compression by adjacent atherosclerotic retinal arteries [2]. Retinal ischemia following vascular occlusion can cause both vitreous and aqueous vascular endothelial growth factor (VEGF) elevation [3]. Thrombosis of the retinal veins causes an increase in retinal capillary pressure resulting in increased capillary permeability and leakage of fluid and blood into the retina. Increased production of vascular endothelial growth factor (VEGF) occurring early in RVO is a major contributor to the evolution and persistence of ME and hemorrhages [4]. In addition, the high levels of VEGF promote the progression of retinal non perfusion and

ischemia, which may in turn increase the levels of VEGF, hence exacerbating ME and hemorrhages leading to visual impairment [5,6]. Not all people with CRVO will require treatment and macular edema will resolve in about a third of those with non-ischaemic CRVO. However, most will need treatment and the number of options has increased in recent years [7]. For many years, laser photocoagulation has been the standard therapy for patients with macular edema secondary to branch retinal vein obstruction (BRVO) [8]. However, laser treatment was not found to be beneficial to those with macular edema secondary to CRVO, for these patients, no therapeutic modalities could be offered [9].

Recently, several studies have demonstrated the benefit of anti-vascular endothelial growth factor (VEGF) therapies and steroids for the management of patients with

macular edema secondary to CRVO [10]. Intravitreal injections of anti-VEGF, such as bevacizumab (Avastin™, Genentech Inc., South San Francisco, CA, USA) and aflibercept (Eylea™, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA, and Bayer Pharma AG, Berlin, Germany), can effectively reduce the intraocular level of VEGF and hence, reduce the vascular permeability related to macular edema in RVO [6]. Aflibercept (Eylea®, Regeneron, Tarrytown, NY, USA) is the newest anti-VEGF drug that has been approved for the treatment of macular edema due to RVO. This recombinant fusion protein, composed of extra-cytoplasmic, native-receptor VEGF-binding sequences from

VEGF receptor (VEGFR)1 and VEGFR2 [11], binds VEGF165 100 times tighter than either bevacizumab or ranibizumab, and also binds isoforms of VEGF-B and placental growth factor [12]. The VIBRANT trial demonstrated that aflibercept was superior to laser photocoagulation in eyes with BRVO [6], and the COPERNICUS and GALILEO trials showed that aflibercept was superior to sham in eyes with CRVO [13,14].

The most common side effects reported in patients receiving EYLEA are increased redness in the eye, eye pain, cataract, moving spots in the field of vision, increased pressure in the eye, and vitreous (gel-like substance) detachment.

#### PATIENTS & METHODS

This prospective, non-randomized clinical study was performed at Al- Azher University Hospitals and included 60 eyes of 60 patients with macular edema secondary to RVO for the first time. Thirty patients had branch RVO (BRVO) and 30 had central RVO (CRVO). Only one eye from each patient was included in this study. Their ages range from 45y<sub>s</sub> to 71y<sub>s</sub> with the mean of age 56.3±8.15 yrs. Forty six eyes were phakic & 14 were pseudo-phakic before injection. The majority of patients (70%) known to be hypertensives and controlled by medical treatment. **The study was approved by the Ethics Board of Al-Azhar University.**

#### Exclusion criteria included

- (1) Patients with macular edema from causes other than RVO.
- (2) Diminution in visual acuity from causes other than RVO.

- (3) Any history of trauma, previous intravitreal injections, vitreo-retinal surgeries, retinal or macular laser.
- (4) Ocular inflammation in one or both eyes.
- (5) Uncontrolled glaucoma.

Macular edema can be defined as macular leakage on fundus fluorescein angiography and central macular thickness (CMT) more than 250µm detected by optical coherence tomography. All the patients were subjected to complete preoperative ophthalmic assessment; detailed history including the age, sex and duration of symptoms, best corrected visual acuity for near and distance, intraocular pressure measurement with applanation tonometry, slit-lamp examination of the anterior segment, indirect ophthalmoscopy, fundus fluorescein angiography (FFA), and optical coherence tomography (OCT) were done to all patients. Once the diagnosis had been confirmed, and after detailed explanation of risks and benefits of these medications, all the patients signed an informed consents before injection. After instillation of topical anesthesia and povidone-iodine solution onto the conjunctiva, a sterile retractor of eyelid was applied, aflibercept (2mg/0.05ml) was injected through the sclera (3.5–4 mm posterior to the limbus) into the mid-vitreous. After injection, antibiotic drop and ointment were applied to the conjunctival sac and the eye bandaged for 1 day, then the patient was adviced to instill one drop of an antibiotic into the injected eye four times daily for one week after injection.

All patients were followed up monthly during the follow up period for at least 6 months after injection. Follow up was scheduled as follows: 1<sup>st</sup> month, 3<sup>rd</sup> month and 6<sup>th</sup> month.

At every visit the following items should be assessed.

- Best corrected visual acuity.
- Anterior segment examination.
- Assessment of IOP by applanation tonometry.
- Fundus examination.
- Fundus fluorescein angiography at the 3<sup>rd</sup> and the 6<sup>th</sup> months.
- OCT images were also taken at the 1<sup>st</sup>, 3<sup>rd</sup> and the 6<sup>th</sup> month to assess the central macular thickness.

#### Further injections may be needed if:

- a) The BCVA got worse or
- b) The CMT more than 250 µm or

c) There was sub-retinal fluid affecting the visual outcome even if CMT is less than 250µm.

**Statistical analysis**

Statistical analysis were performed using SPSS version 22 (IBM Corporation, Chicago, IL, USA) Snellen BCVA values were converted into LogMAR for statistical analysis. Mean and Standard deviation were estimated. CMT and BCVA were assessed with the ANOVA test followed by tukey test and P-values of < 0.05 were considered statistically significant.

**RESULTS**

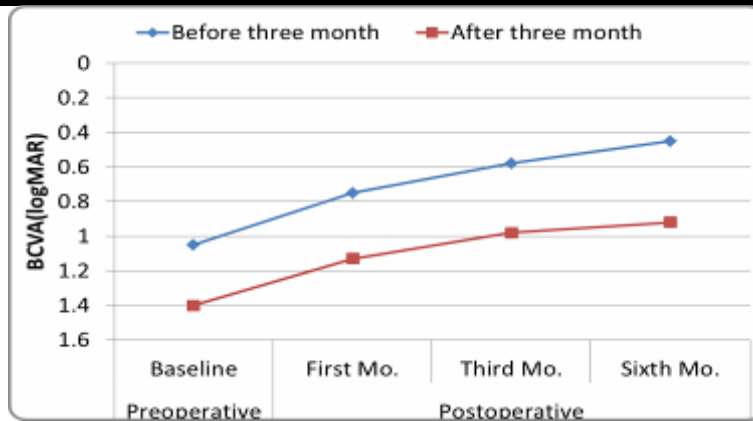
Sixty eyes of 60 patients were enrolled in this study. Patients were equally divided; 30 patients had branch RVO (BRVO) and other 30 had central RVO (CRVO). The demographic data of patients revealed that 44 patients

(73.3%) were males and 16 (26.7%) were females. Age of patients included ranged from 45y<sub>s</sub>, to 71y<sub>s</sub>, with the mean age of 56.3±8.15 yrs. Only one eye of each patient was included in this study. There were no statistically significant differences regarding the age, gender, lens status, laterality. One month after IV aflibercept injection in patients with RVO ≤ 3 months, the main best-corrected visual acuity improved from 1.05±0.004 µm at baseline to 0.75±0.07 logMAR at 1 month, to 0.58±0.10 logMAR at 3<sup>rd</sup> month and by the end of 6th month improved to 0.45±0.14 logMAR (p≤0.05). On the other hand, the mean BCVA improved from 1.40±0.03 µm at baseline to 1.13±0.07 logMAR at 1 month, to 0.98±0.06 logMAR at 3<sup>rd</sup> month and to 0.92±0.08 logMAR at 6<sup>th</sup> month (P≤ 0.05) in patients with RVO > 3 months (table 1 and figure 1).

**Table (1):** The mean BCVA at base line and after 1<sup>st</sup>, 3<sup>rd</sup>, 6<sup>th</sup> months of aflibercept injection in patients with RVO.

\*cells in rows with different letter were significant differences at p ≤ 0.05 (LSD).

Duration	Baseline	1 <sup>st</sup> Mo.	3 <sup>rd</sup> Mo.	6 <sup>th</sup> Mo.
Before three months	1.05±0.004 <sup>a</sup>	0.75±0.07 <sup>b</sup>	0.58±0.10 <sup>c</sup>	0.45±0.14 <sup>d</sup>
After three months	1.40±0.03 <sup>a</sup>	1.13±0.07 <sup>b</sup>	0.98±0.06 <sup>c</sup>	0.92±0.08 <sup>d</sup>



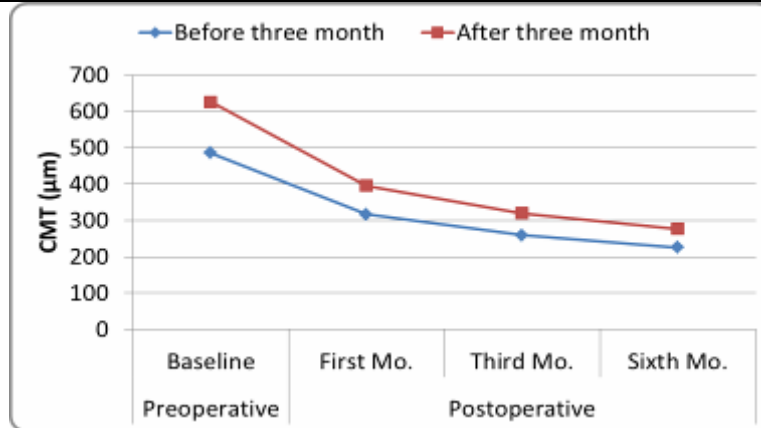
**Figure (1):** The mean BCVA at base line and after 1<sup>st</sup>, 3<sup>rd</sup>, 6<sup>th</sup> months of aflibercept injection in patients with RVO.

The mean central macular thickness reduced from 485.57±71.51µm at baseline to 316.78±58.38µm (P≤0.05) after 1 month, at the 3rd month reduced to 259.45±50.84µm (P≤0.05) and by the end of 6th month reduced to 225.85±34.44µm (P≤0.05) in those with RVO ≤ 3 months. Whereas, in those with RVO > 3 months the main CMT reduced from baseline 625.91±167.56µm to 395.07±98.89µm (P≤0.05), 3rd month after injection reduced to 319.53±53.28µm P≤0.05) and by the end of 6<sup>th</sup> month reduced to 276.50±38.89 µm (p≤0.05) (table 2 & figure 2). The injection was well tolerated in all patients. No evidence of intra-operative or post-operative complications as retinal detachment, vitreous hemorrhage, or elevated intraocular pressure. prolonged delay in treatment is associated with less improvement in the visual acuity. Local hyperemia or subconjunctival hemorrhage may be noticed at the site of injection in some cases.

**Table (2):** The mean central macular thickness at base line and after 1<sup>st</sup>, 3<sup>rd</sup>, 6<sup>th</sup> months of aflibercept injection in patients with RVO.

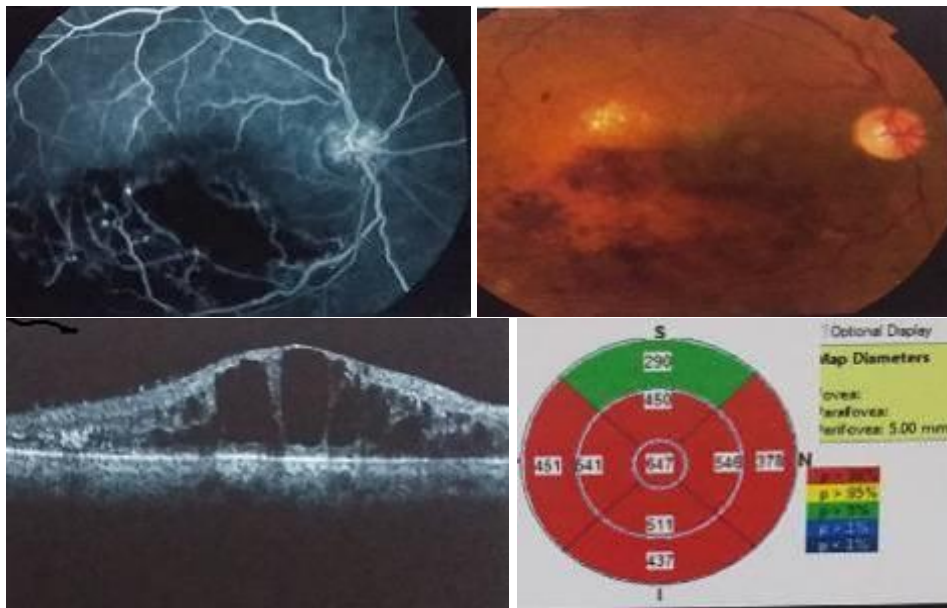
\*cells in rows with different letter were significant differences at  $p \leq 0.05$  (LSD).

Duration	Baseline	1 <sup>st</sup> Mo.	3 <sup>rd</sup> Mo.	6 <sup>th</sup> Mo.
Before three months	485.57±71.51 <sup>a</sup>	316.78±58.38 <sup>b</sup>	259.45±50.84 <sup>c</sup>	225.85±34.44 <sup>c</sup>
After three months	625.91±167.56 <sup>a</sup>	395.07±98.89 <sup>b</sup>	319.53±53.28 <sup>c</sup>	276.50±38.89 <sup>d</sup>

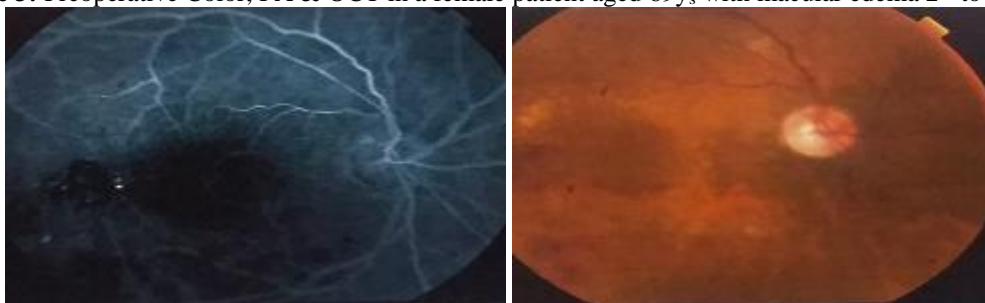


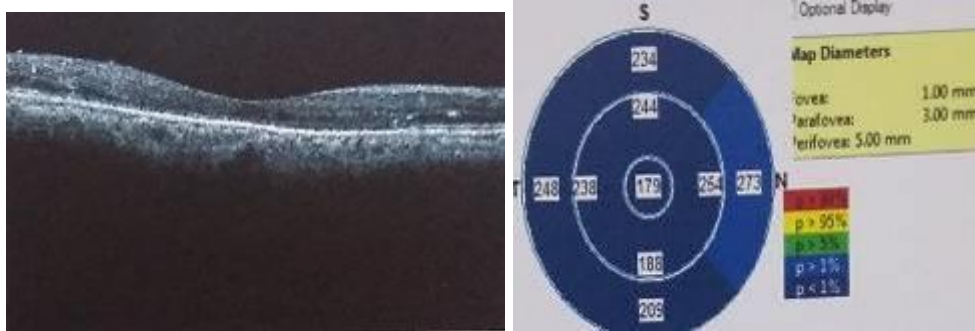
**Figure (2):** The mean central macular thickness at base line and after 1<sup>st</sup>, 3<sup>rd</sup>, 6<sup>th</sup> months of aflibercept injection in patients with RVO.

**Case No. 1**



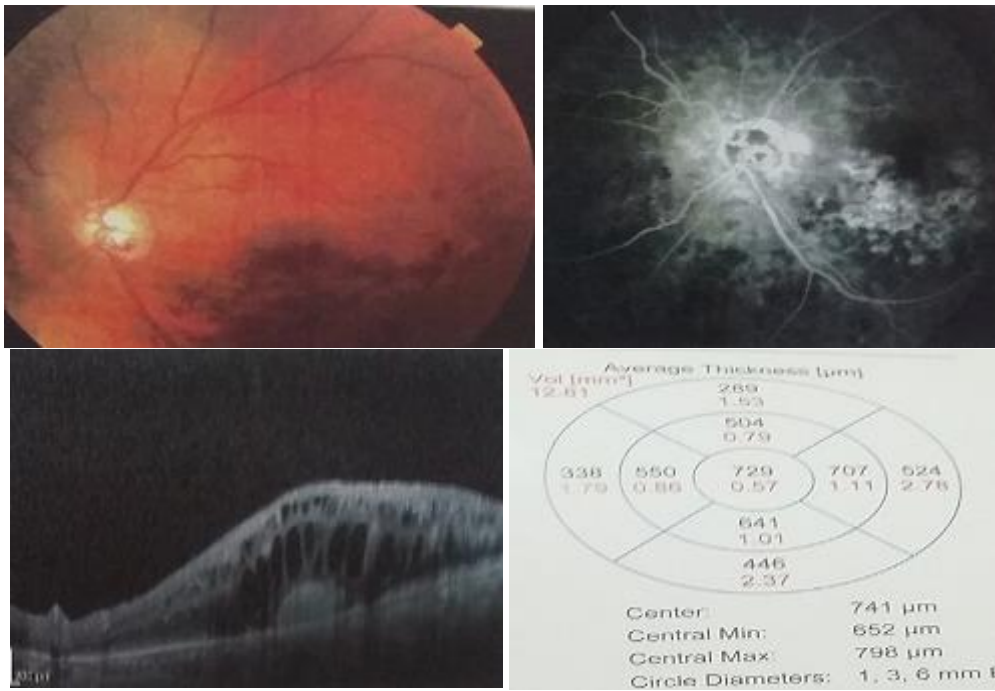
**Figure 3:** Preoperative Color, FA & OCT in a female patient aged 69y, with macular edema 2<sup>o</sup> to BRVO.



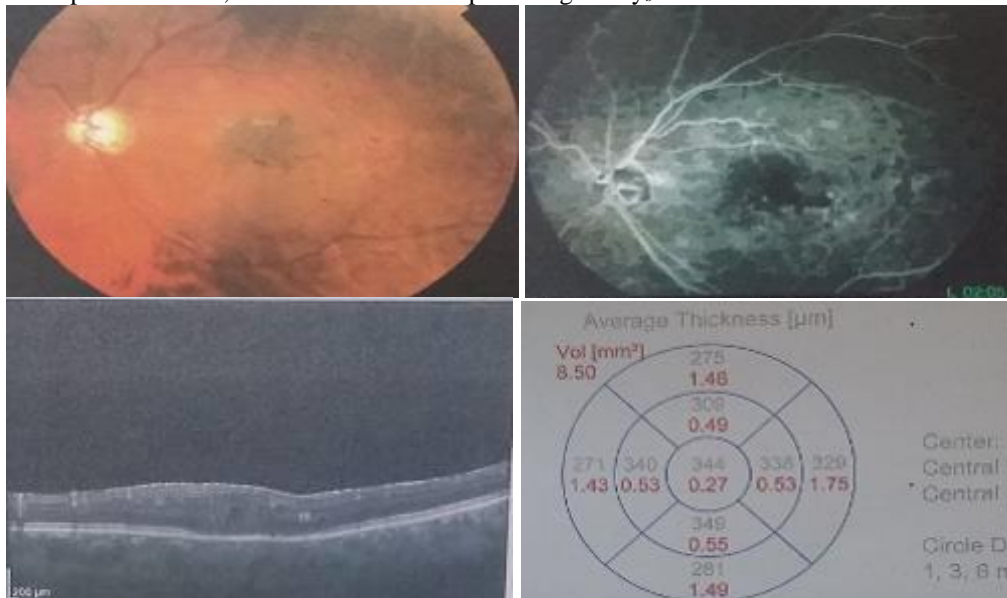


**Figure 4:** 6 months postoperative Color, FA & OCT of the same patient revealed Complete resolution of the macular edema.

**Case No. 2**



**Figure 5:** Preoperative Color, FA & OCT in a male patient aged 71y with macular edema 2<sup>y</sup> to BRVO.



**Figure 6:** 6 months postoperative Color, FA & OCT of the same patient revealed complete resolution of the macular edema.

## DISCUSSION

Retinal vein occlusions (RVOs) are the second most common retinal vascular diseases after diabetic retinopathy. RVO affects approximately one to two percent of adults over the age of 40 [15,16]. While BRVO is four times more common than CRVO, however, CRVO is considered the most significant threat to vision [17]. The standard of care for macular edema secondary to branch retinal vein occlusion (BRVO) has been guided since 1984 by the findings of the Branch Vein Occlusion Study, which showed that macular photocoagulation was superior in improving visual acuity compared with observation [8]. The 1995 Central Vein Occlusion Study (CVOS) concluded that grid laser treatment of macular edema was of no visual benefit despite the elimination of macular edema in treated eyes [9]. Since then, new pharmacologic agents have changed the treatment paradigm of macular edema secondary to RVO. There are 3 treatment options recently approved by the Food and Drug Administration (FDA) for treatment of macular edema secondary to RVO. These include a dexamethasone intravitreal implant (Ozurdex, Allergan), ranibizumab (Lucentis, Genentech), and aflibercept (Eylea, Regeneron). Intravitreal injection of anti-VEGF has been shown to be a new promising treatment modality, which results in noticeable functional and anatomical improvement. Aflibercept is a decoy receptor fusion protein, composed of the second domain of human VEGF receptor 1 and the third domain of VEGF receptor 2, which are fused to the Fc domain of human IgG1. Aflibercept can downregulate VEGF-A, VEGF-B, and placental growth factor, which are synergistic for pathologic angiogenesis [18]. Aflibercept revealed superior anti-VEGF capability than bevacizumab in vitro. The binding affinity of VEGF for this drug is higher than for ranibizumab and bevacizumab, also it displays a prolonged VEGF inhibition in comparison with the other VEGF- antagonists in retinal pigment epithelium/choroid organ cultures [12,19].

In a randomized controlled trial, aflibercept was compared with bevacizumab for treatment of diabetic macular edema. The authors concluded that aflibercept was more effective than bevacizumab for visual improvement in diabetic patients with poor baseline vision, but comparable efficacy in both pharmaceutical agents for better baseline vision. Both

medications showed similar safety profiles and injection number during one-year follow-up [20].

The Phase III registration trials demonstrated that intravitreal aflibercept is superior to standard-of-care for the treatment of macular edema due to BRVO and CRVO [21].

In our study, 60 eyes of 60 patients with macular edema due to RVO received a single intravitreal aflibercept injection revealed marked resolution of macular edema and improvement of visual acuity. Also, this study stated that improvement in vision and CMT depends on the duration of the disease, so greater improvement in vision and CMT noticed in those diagnosed and treated earlier than others and this coinciding with results of several studies which stated that the effect of anti-VEGF agents on macular edema secondary to RVO occurs very soon after the initiation of treatment with improvement of both BCVA and CMT. However, improvement in visual acuity disproportionate to the amount of reduction in macular edema. Larger RVO trials suggest that even brief periods of under-treatment (as short as 6 months) may result in poorer long-term visual outcomes [14,21]. Also, our results support the results of other studies stated that RVO patients should be followed closely and regularly, so that recurrent edema can be treated promptly. Additional injections may be needed based on OCT findings especially in those with long term duration & massive macular edema as single injection wasn't sufficient.

## CONCLUSION

*Our study in the short term follow up period, concluded that:*

- 1- Intravitreal injection of aflibercept is more clinically effective and safe for treatment of macular edema 2<sup>ty</sup> to RVOs and is generally well tolerated.
- 2- Good long-term anatomical & functional outcomes could be obtained if the treatment started as early as possible.

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