Comparison of Therapeutic Efficacy on Grid Laser Photocoagulation Combined with Aflibercept and Ranibizumab as Pro re Nata Regimen for Macular Edema Secondary to Branch Retinal Vein Occlusion

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ABSTRACT

Purpose: To compare the therapeutic efficacy of grid laser photocoagulation (GLP) with intravitreal aflibercept (IVA) versus ranibizumab (IVR) on eyes with macular edema (ME) due to branch retinal vein occlusion (BRVO).

Methods: A total of 139 patients (139 naive eyes) with ME caused by BRVO which was received therapy for IVA combined with GLP (72 eyes) against IVR combined with GLP (67 eyes), retrospectively reviewed. Main outcomes for best corrected visual acuity (BCVA), central foveal thickness (CFT), central foveal volume (CFV) and subfoveal choroidal thickness (SFCT) were recorded from baseline to final visit. Spectral-domain optical coherence tomography (SD-OCT) and fundus fluorescein angiography (FFA) were used to show anatomic findings. GLP was implemented over the focal leaks seen on the FFA that used a 532 nm diode laser system. BRVO was classified as ischemic and non-ischemic according to FFA findings.

Results: The mean age was 65.49 ± 9.59 years (range; 45 - 87 years) and mean follow-up time was 37.95 ± 13.29 months (range; 13 - 60 months). Average IVA and IVR injection counts from baseline to final visit were 3.84 ± 1.85 (range; 1 to 9) and, 4.89 ± 2.49 (range; 1 to 10) respectively (p=0.011). Mean counts of GLP in IVA and IVR groups from baseline to final visit were 3.4 ± 1.2 (range; 2 to 8) and, 3.5 ± 1.1 (range; 2 to 7), respectively (p=0.610). The mean CFT decreased from baseline to final visit were 537.40 ± 181.84 µm to 266.43 ± 51.89 µm in the IVA group, and 528.94 ± 177.52 µm to 312.59 ± 78.15 µm in the IVR group (p<0.001). Mean BCVA changes from baseline to final visits were 1.00 ± 0.55 to 0.40 ± 0.36 Logarithm of the Minimal Angle of Resolution (logMAR) in IVA group, and 0.96 ± 0.54 to 0.45 ± 0.38 logMAR in IVR group, respectively (p<0.001). A statistically significant improvement was detected in CFV and SFCT when compared to the baseline in all follow-up visit in both group (p<0.001). Epiretinal membran gelişimi ve başlangıçta seröz retina dekolmanı varlığı açısından iki grup arasında anlamlı bir fark yoktu (p>0.05). There was no statistically significant difference in both CFT and BCVA in eyes with ischemic and non-ischemic BRVO at both group (p>0.05).

Conclusion: Combination therapy with GLP through either IVA or IVR was found to be effective in treatment of ME due to BRVO. Number of injections was less in IVA group than IVR group. Anatomical recovery was observed more in the IVA group.

Keywords: Branch retinal vein occlusion, Aflibercept, Ranibizumab, Macular edema, Grid laser photocoagulation.

INTRODUCTION

Branch retinal vein occlusion (BRVO) is a retinal vascular disorder which is common after diabetic retinopathy, and may cause loss of vision.[1-3] BRVO often appears in the arteriovenous crossover region where both vessels participate into the common adventitia. The most common concurrent factors that affect the vision in the short and long term follow-up include retinal hemorrhages, macular ischemia, and macular edema (ME).[4,5] ME is the most significant complication affecting the visual quality and acuity in BRVO.[6]

In previous studies, 60% of eyes with ME has progressed to chronic form, and 86% of patients with chronic ME presented a vision at 20/50 or worse.[2,7] There has been various promising treatment methods for ME.[2,6] One

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of such methods is grid or focal laser photocoagulation in order to treat recalcitrant ME has been approved as the standard form of care. Nevertheless, efficacy of this method on vision were variable.[5,8-10] Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents have currently been used to treat ME due to retinal vein occlusion (RVO).[9,11-13] However, these agents are eliminated by the vitreous cavity, and cause ME after a few months; therefore, the procedure should be repeated on regular basis.[2,9,11-14]

The aim of the present study was to assess the visual and anatomical results of grid laser photocoagulation (GLP) through IVR or IVA injections in eyes with ME due to BRVO.

MATERIALS AND METHODS

Medical records of 139 eyes of 139 patients who had GLP by IVA and IVR injections for ME due to BRVO between January, 2014 and January, 2020 were analysed, retrospectively.

Patients were divided into two groups including 72 eyes treated by IVA in Group 1, and 67 eyes treated by IVR in Group 2. In addition, patients were divided into 2 subgroups as ischemic and non-ischemic BRVO according to FFA results, and the efficacy of both anti-VEGF agents was compared in these subgroups.

Principles of the Helsinki Declaration were followed during the study. The study protocol was approved by the ethics committee of Sadi Konukoglu Hospital, Istanbul. All patients enrolled into the study were diagnosed with ME caused by BRVO and subsequent decreased visual acuity due to this situation. Eyes with ischemic BRVO which was ≥ 5 disc area on the posterior and peripheral pole were excluded from the study. Naive BRVO patients diagnosed with ME within last 3 months and received monotherapy for BRVO were included into the study.

The patients with concomitant systemic diseases which have caused macular dysfunction including retinal disease (i.e. age-related macular degeneration (AMD), diabetic retinopathy, epiretinal membrane (ERM), macular hole (MH), macular ischemia) and media opacities that could be reduced visual acuity were excluded. Furthermore, the patients diagnosed with BRVO without ME were also excluded. HbA1c and renal function values of patients with ME due to BRVO who had diabetes mellitus (DM) were within normal limits. Patients who were suspected of anti-VEGF resistance and changed treatment or were treated with subtenon steroid/intravitreal dexamethasone implant/ intravitreal triamcinolone were excluded from the study. The data of the patients included best corrected visual acuity (BCVA), subfoveal choroidal thickness (SFCT), central foveal volume (CFV), central foveal thickness (CFT), and intra-ocular pressure (IOP) which were detected at baseline and at the 3rd, 6th, 12th months and final visits. Number of intravitreal injections were recorded for every patient. IOP was measured through Goldmann applanation tonometry by a physician and ophthalmic examinations were performed by using a slit lamp microscopy with 90 diopter non contact lens. Fundus imaging was performed by fundus fluorescein angiography (FFA) (HRA-2, Heidelberg Engineering, Heidelberg, Germany) and spectral domain-optical coherence tomography (SD-OCT) (Spectral Domain OCT, Cirrus Zeiss, and Heidelberg Spectralis, Heidelberg Engineering), before and during follow-up. Repetition of FFA was decided when there was no evidence for BCVA decline by ocular examination and other imaging techniques. The mean foveal thickness was described as in the central 1 mm diameter region which was calculated with the early treatment diabetic retinopathy study (ETDRS) mapping software system provided by SD-OCT device. FFA was performed for leakage areas in the retinal capillaries at fovea and peripheral retina which were determined to be the cause of ME. All examinations were performed between 8.00 a.m. and 11.00 a.m. due to diurnal changes of choroidal blood flow. The distance between the base edge of the subfoveal retinal pigment epithelium (RPE) and the border of the choroidoscleral junction was defined as SFCT; and vertical line scans were performed for each eye beneath the fovea.

Intravitreal procedures were carried out under sterile conditions. Intravitreal injections were performed through a 30 gauge needle at a distance of 4 mm from the temporal limbus in phakic eyes and 3.5 mm in pseudophakic eyes.

Treatment protocol

Initially, aflibercept (2mg/0.05mL) and ranibizumab (0.5mg/0.05mL) were injected separately in each group; it was followed by intravitreal pro re nata (PRN) [15] regimens on monthly basis. The participants were assessed on monthly basis and PRN regimen was performed according to the protocol of re-treatment criteria at the 6th, 12th month and final visit. PRN regimen was implemented according to the regulated re-treatment criteria. None of the participatiants in the study had no switch between injections. A detailed written informed consent form was given to the patients and it was left to the patient's final decision about drug selection.

Criteria for re-treatment of anti-VEGF injections

The criteria for re-treatment included persistent or worsened ME following PRN regimen, and impairement of visual

acuity compared to the prior visit; in such cases injection was decided to be performed on monthly basis. When there was not any change in macular thickness or visual acuity in two consecutive visits, treatment was discontinued.

Recovery or worsening of ME was characterized as follows;

1. A change (increase or decrease) by at least 10% in CFT when compared to the previous visit.

2. Any change (increase or decrease) up to 0.1 decimal in visual acuity in comparison with previous visit was accepted as a change.

When at least one of the re-treatment criteria was observed, patients in the IVA and IVR groups were re-treated on monthly basis.

Grid Laser Photocaoagulation

Focal leakage and wider retinal thickening areas were visualized with FFA; and GLP was subsequently performed by 532 nm diode laser system. The GLP settings as: spot diameter,50 µm; exposure time, 0.1 seconds; and power 100-200 mW. A period of 1 week in ischemic BRVOs, and 1 month in non-ischemic BRVOs was allowed for GLP in consideration of reperfusion. GLP procedure was performed 1 week after anti-VEGF injections in ischemic BRVO and 1 month after anti-VEGF injections in non-ischemic BRVO. Following the initial GLP treatment, patients were evaluated for additional GLP requirement at 2-month intervals.

Criteria for re-treatment of Grid Laser Photocoagulation

1. Grid laser photocaoagulation was performed when new focal leakage or diffuse retinal thickening areas were detected by FFA and OCT.

2. Snellen visual acuity of ≤20/40

3. CFT≥ 250 µm

4. Visual acuity gain of <0.1 decimal compared to baseline.

Statistical Analysis

The BCVA was examined with Snellen chart and values obtained were converted into the Logarithm of the Minimal Angle of Resolution (logMAR) for statistical analysis. Distribution of data was determined by using Shapiro-Wilk test. Continuous variables were defined as mean ± standard deviation whereas categorical variables were expressed infrequency and percentage. Independent t test was used to compare the data between two groups. The data changes during follow-up period were evaluated through MANOVA test. Pearson's correlation test was used to assess the association between non-parametric variables.The change in BCVA, CFT and CFV during follow-up period were analyzed by paired sample t test. Chi-square test was used to analyze nominal parameters between groups. SPSS (version 22.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A p value below 0.05 ($p < 0.05$) was accepted as statistically significant.

RESULTS

The mean age was 65.49 ± 9.59 years (range; 45 - 87 years) and the mean follow-up time was 37.95 ± 13.29 months (range; 13 - 60 months). Seventy three (52%) patients were male; 66 (48%) patients were female. Among patients' eyes, 73 (52%) eyes were phakic, 66 (48%) eyes were pseudophakic; and 75 (53%) eyes were on the right side whereas 64 (47%) eyes were on the left side. Seventeen eyes were excluded due to poor OCT image quality (n = 12) and chorioscleral interface that could not be imaged (n=5). Furthermore, seven eyes were excluded due to macular diseases such as MH (n=3) and choroidal neovascular membrane (n=4).

There were not any significant differences in age (p=0.077), side (p=0.508), follow-ups (p=0.740), gender (p=0.057), baseline BCVA (p=0.685), CFT (p=0.820), SFCT (p=0.897), CFV (p=0.434) and IOP (p=0.083) between the 2 groups.

It was found statistically that there was no difference in results between patients with or without DM, and it was determined that patients with DM did not affect the results ($p > 0.05$). The clinical and demographic data of the study is summarized in Table 1.

There was a statistically significant decrease in BCVA, CFT, SFCT and CFV when compared to the baseline in both groups during all follow-ups ($p < 0.05$).

Group 1(IVA),

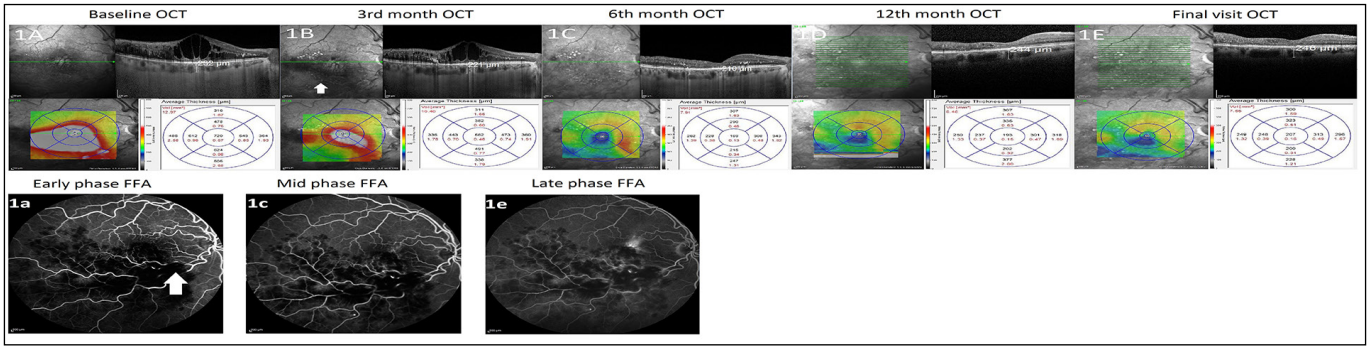
In the IVA group, the mean follow-up time was 33.59 ± 13.21 months (range; 13 to 60 months). The mean injection count was 3.84 ± 1.85 (range, 1 to 9) and, mean GLP count was 3.4 ± 1.2 (range; 2 to 8), respectively.

There was a significant decrease in BCVA (log MAR), CFT, and CFV than the baseline in all follow-up visits ($p < 0.001$). Statistically significant changes were found in SFCT during all follow -ups when compared to baseline ($p < 0.05$). Figure 1 shows OCT and FFA image of a patient who had IVA injection.

Table 2: *The results of the study according to the follow-up periods*

Groups		Baseline	3rd month	6th month	12th month	Final visit	p values*
Group 1	BCVA	1.00 ± 0.55	0.75 ±0.57	0.57±0.47	0.45 ± 0.39	0.40 ±0.36	<0.001*
aflibercept	CFT	537.40 ± 181.84	288.96 ± 70.00	296.40 ± 81.47	287.27 ± 72.10	266.43 ± 51.89	<0.001*
	CFV	11.61 ± 2.12	9.05 ±1.02	9.16 ± 1.11	8.99 ± 1.31	9.01 ±1.24	0.028*
	SFCT	247.55 ±38.86	237.59 ± 37.26	236.82±36.78	237.26±37.42	231.61±34.90	0.019*
	IOP	16.07 ± 2.40	16.61 ± 2.04	16.21 ± 2.26	16.01 ±2.68	16.44±2.05	0.35
Group 2	BCVA	0.96 ± 0.54	0.68 ± 0.53	0.54 ± 0.43	0.47 ± 0.38	0.45 ± 0.38	<0.001*
ranibizumab	CFT	528.94 ± 177.52	299.76 ± 74.74	312.26 ±79.92	307.28 ± 85.25	312.59 ± 78.15	<0.001*
	CFV	11.30 ± 1.87	8.95 ± 0.75	8.87±0.86	8.64 ± 0.70	8.47 ± 0.63	0.01*
	SFCT	249.65 ± 39.06	224.05 ± 38.86	226.47±41.68	222.27 ± 39.54	236.40 ± 41.01	0.031*
	IOP	16.94 ± 2.70	16.52 ± 1.99	16.23±1.75	16.01 ± 2.01	16.85 ± 2.39	0.15

*MANOVA test
BCVA, best corrected visual acuity; CFT, central foveal thickness; CFV, central foveal volume; SFCT, subfoveal choroidal thickness, IOP, intra-ocular pressure

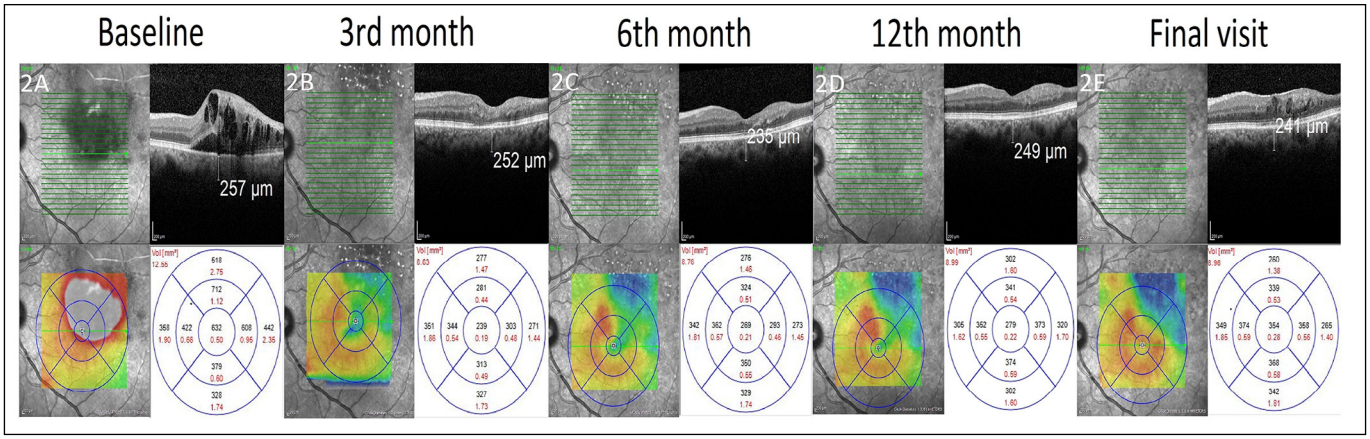


Figures 1: *An optical coherence tomography (OCT) image of a patient who had intravitreal aflibercept (IVA) injection. The white arrow shows laser spots observed in Figure 1B. The fundus fluorescein angiography (FFA) image of the same patient who had IVA injection. The white arrow in Figure 1a points out the occlusion region in FFA.*

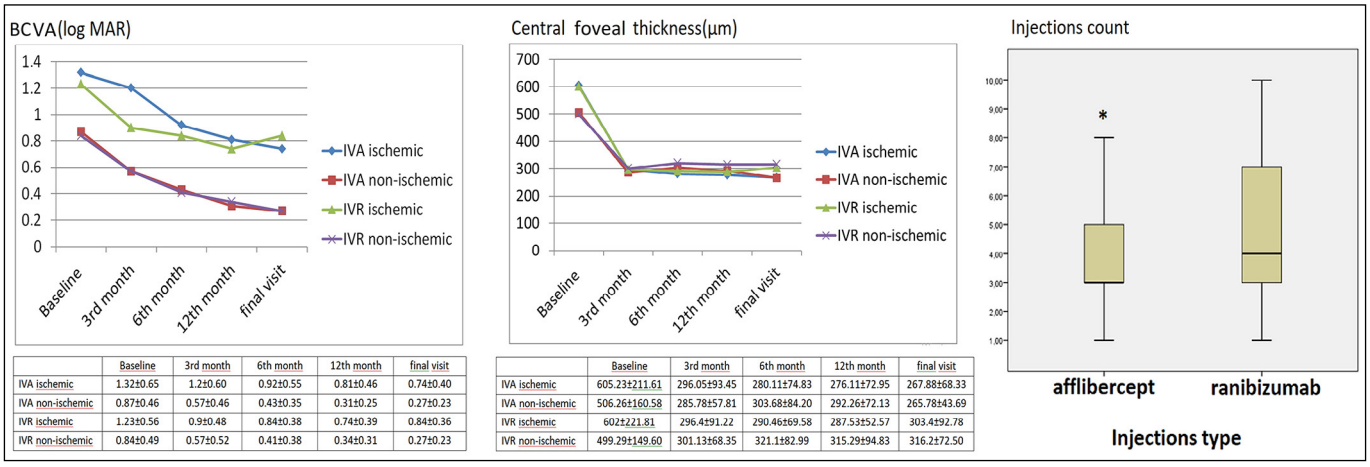
Group 2(IVR),

In the IVR group, the mean follow-up time was 38.18 ± 13.11 months (range; 13 to 56 months). The mean injection count was 4.89 ± 2.49 (range; 1 to 10), and mean GLP count was 3.5 ± 1.1 (range; 2 to 7), respectively.

A statistically significant improvement was detected in BCVA, CFT, CFV, and SFCT when compared to the baseline in all follow-up visits (p<0.001). Figure 2 shows OCT and FFA image of a patient who had IVR injection. Changes of BCVA, CFT and count of injections according to the groups and follow-up visits are presented in Figure 3.



Figures 2: *Representative SD-OCT images according to the follow-up period of a patient in the IVR group.*



	Baseline	3rd month	6th month	12th month	final visit
IVA ischemic	1.32±0.65	1.2±0.60	0.92±0.55	0.81±0.46	0.74±0.40
IVA non-ischemic	0.87±0.46	0.57±0.46	0.43±0.35	0.31±0.25	0.27±0.23
IVR ischemic	1.23±0.56	0.9±0.48	0.84±0.38	0.74±0.39	0.84±0.36
IVR non-ischemic	0.84±0.49	0.57±0.52	0.41±0.38	0.34±0.31	0.27±0.23

	Baseline	3rd month	6th month	12th month	final visit
IVA ischemic	605.23±211.61	296.05±93.45	280.11±74.83	276.11±72.95	267.88±68.33
IVA non-ischemic	506.26±160.58	285.78±57.81	303.68±84.20	292.26±72.13	265.78±43.69
IVR ischemic	602±221.81	296.4±91.22	290.46±69.58	287.53±52.57	303.4±92.78
IVR non-ischemic	499.29±149.60	301.13±68.35	321.1±82.99	315.29±94.83	316.2±72.50

Figures 3: *Changes in corrected distance visual acuity (BCVA), central macular thickness and count of injections by follow-up periods in both groups.*

When the both group were compared for the number of injections, it was statistically and significantly lower in the IVA group (p=0.011). Continuity of photoreceptors were detected in non-ischemic BRVO; however, integrity of photoreceptors were disrupted in ischemic BRVO (r= 0.348, p<0.001). Although ERM formation was detected in ischemic BRVO, no formation was observed in non-ischemic BRVO (r=-0.243, p=0.012). Baseline BCVA values were better in non-ischemic BRVOs (r=0.229, p=0.018). The most important factors that affect the final BCVA were continuity of photoreceptors (r=0.336, p<0.001), non-ischemic BRVO (r=0.597, p<0.001), and baseline BCVA (r=0.376, p<0.001). The most important factor triggering ERM formation in the final follow-up visit was ischemic BRVO (r=-0.243, p=0.012). Serous retinal detachment (SRD) formation was frequently observed in ischemic BRVOs (r=-0.216, p=0.026); and if SRD was present in the baseline visit, the initial BCVA was observed to be lower (r=-0.379, p<0.001). Except for the final visit, there was not any difference between two groups in BCVA, CFT, CFV, and SFCT during all visits (p> 0.05). In the final visit, a statistically significant reduction was detected in CFV (p=0.006), and SFCT (p=0.042) in the IVR group when compared to the IVA group. However, CFT values were significantly lower in the IVA group compared to the IVR group at the final visit (p=0.001). However, no difference was observed in BCVA in both groups during final examination (p=0.536). No statistical relationship was detected between SFCT and BCVA (p>0.05).

The mean number of GLP treatments at final visit was 3.4±1.2 (range; 2 to 8) in the IVA group and 3.5±1.1 (range; 2 to 7) in the IVR group (p = 0.610).

In 7 (%9) eyes in IVA group, 9 (%13) eyes in IVR group, phacoemulsification surgery was performed during the follow-ups, respectively. Performing cataract surgery during the follow-up periods in both groups did not cause a statistically significant change in anatomical and visual results (p>0.05).

In ischemic BRVO, 0.84 ± 0.47 logMAR in the IVR group, 0.76 ± 0.42 logMAR in the IVA group, and no statistically significant difference was observed (p=0.459). In terms of CFT, there was no significant difference in IVR group (300.07 ± 75.29 µm) versus in IVA group (279.94 ± 64.31 µm) (p=0.617).

In non-ischemic BRVO, 0.28 ± 0.16 logMAR in the IVR group, 0.27 ± 0.14 logMAR in the IVA group and no statistically significant difference was detected (p=0.892). In terms of CFT, there was no significant difference in IVR group (312.49 ± 82.67 µm) versus in IVA group (280.38 ± 66.49 µm) (p=0.491).

In our study, 8 (11%) eyes in IVA group, 6 (9%) eyes in IVR group had transient IOP elevation but returned to normal limits with medical treatment group, respectively. In 7 (9%) eyes in IVA group, 9 (13%) eyes in IVR group, phacoemulsification surgery was performed during the follow-ups, respectively. There was no statistically significant difference in the efficacy of anti-VEGFs in both BCVA and CFT in phakic and pseudophakic eyes, separately (p>0.05). Vitreous hemorrhage developed in 4 (5%) eyes in IVA group, 5 (7%) eyes in IVR group during the follow-up period and was resolved with treatment at both groups, respectively. The results of the study according to the follow-up visits are summarized in Table 2.

DISCUSSION

The prevalence of RVO currently varies between 0.7% and 1.6%, and there are two major types of RVO: central RVO and BRVO [2, 16,17]. BRVO is classified in two types: major (major retinal vein branches) and minor

Table 1: *The clinical and demographic informaiton of patients*

Injection type	**Afflibercept**	**Ranibizumab**	**p values**
	Group 1	**Group 2**	
Eyes	72	67	
Sex	$34^{f}38^{m}$	$32^{f}35^{m}$	
Age (mean ±SD)	64.80±9.46	66.09±9.52	0.761
Side	$39^{r}33^{l}$	$36^{r}31^{l}$	
Lens status (phakic/pseuodphakic)	38/34	35/32	0.879
Hypertension (%)	34(47%)	33(49%)	0.410
Diabetes (%)	12(16%)	14(20%)	0.362
Hyperlipidemia (%)	4(5 %)	5(7%)	
Follow up (months) (mean ±SD)	36.59±13.21	38.18±13.11	0.740
Follow up (months) (range)	13 to 60	13 to 56	
Number of injections (mean ±SD)	3.84±1.85	4.89±2.49	0.011*
Number of injections-range	1 to 9	1 to 10	
Number of GLP (mean ±SD)	3.4±1.2	3.5±1.1	0.610
Time between diagnosis and injection (months)	0.4 ± 0.09	0.3 ± 0.11	0.691
Time between diagnosis and GLP (months)	0.8±0.2	0.7±0.4	0.871
Final visit ERM (presence/absence)	13/59	11/56	0.571
Localization of BRVO (superior/inferior)	42/30	41/26	0.468
Types of BRVO (non-ischemic/ischemic (< 5 OD))	57/15	53/14	0.898
Types of BRVO (major/macular)	60/12	54/13	0.978
Final visit status of photoreceptors (continuity/disrupt)	61/11	55/12	0.374
Baseline SRD (presence/absence)	39/33	39/28	0.569

BRVO, branch retinal vein occlusion; SD, standard deviation; OD, optic disc; ERM, epiretinal membrane; ^{f} female, ^{m} male; ^{r} right, ^{l}left; SRD, serous retinal detachment; GLP, grid laser photocagulation, *Independent t test

(macular venules).[5] Involvement of superotemporal and inferotemporal quadrants in major BRVO was detected by 66%, and 22.43%, respectively.[18] Similar to the literature, we detected superior (58%), inferior (42%) quadrants in IVA group and superior (61%), inferior (39%) quadrants in IVR group. Patients suffered from BRVO which cause painless loss of vision and is usually seen on the areas where arterioles cross the arteries.[5, 18, 19]

Various treatment methods have been used for ME caused by BRVO including laser photocoagulation, intravitreal steroid injections, and vitrectomy.[2, 5-6, 8,10] Among such methods, GLP has become a standard treatment for ME in BRVO according to the results of the BRVO study.[20]

Farese et al. showed in their retrospective study that combination therapy has a long-lasting effect and requires fewer re-injections: GLP was administered 2 weeks following the initial IVR injection and the PRN regimen was used as an anti-VEGF injection protocol. They decided that the most potent anti-VEGF efficacy and hence the greatest decrease in CFT occurred 2 weeks after anti-VEGF implementations, and this time point may be the most influential for laser therapy.[21] In present study, anti-VEGF was implemented when as needed, and GLP was also administered in ischemic and non-ischemic BRVO for 2 weeks and 1 month following the initial injection, respectively.

The effectiveness of the GLP in ME caused by BRVO is controversial. Six months results for BRIGHTER study (IVR vs IVR with laser vs solely laser) showed performing IVR as a PRN regimen following monthly three loading doses with or without GLP demonstrated a significant improvement in BCVA compared with laser alone in eyes with BRVO.[22] Also these results were approved by 2-year results.[23] The BRIGHTER study were almost consistent results in addition to other studies like as BRAVO,[24] HORIZON,[25] SHORE,[15] and RETAIN[26] that pointed out benefical effects of long-term course of ranibizumab therapy in BRVO patients. Özkurt et al. reported that IVR or yellow subthreshold micropulse laser therapy in ME secondary to BRVO did not surpass to each other in decrement of CFT and improving BCVA during 1 year follow up. According to their results, they claimed that the subthreshold micropulse laser therapy could be an effective alternative option in the treatment of ME secondary to BRVO.[27]

The GLP combined with IVR has a prominent efficacy on improving visual acuity in ME caused by BRVO.[28,29] Salinas-Alaman et al. reported to effective results that was performed the combination of IVR and GLP in eyes with ME secondary to BRVO.[30] However, the lack of a control group constitutes the limitation of their study.

A prospective study by Narayanan R et al. showed the efficacy of GLP combined with IVA or IVR for treatment in naive eyes of BRVO with ME. Criteria for repetition included a decrease of five letters or more in visual acuity, and existence of persistant intra- or subretinal fluid in OCT. In case of fluid in SD-OCT, GLP was repeated when laser indications were achieved at least 3 months later. Assessments of two-months intervals after first 6 months with a need of less PRN injections were effective to maintain the visual gains within the first 6 months. In the IVA group, a higher number of rescue lasers were needed in month 12 when compared to the IVR group (20 vs 11; $p = 0.06$).[31]

Vascular endothelial growth factor - A is the main angiogenic factor blamed in the pathogenesis of ME due to retinal neovascular disorders. VEGF-A isoform occurs in response to ischemia, hypoxia and inflammation.[32] As an anti-VEGF agent, IVR blocks the increased vascular permeability as a monoclonal antibody fragment against to VEGF, and eventually prevents the development of ME.[22] Aflibercept is a soluble VEGF decoy receptor protein (fusion protein) produced by trap technology that may bind several members of the VEGF family, including VEGF-A, VEGF-B, and placental growth factor (PlGF) which activate VEGFR-1.[33] Therefore, aflibercept may further block the VEGFR-1 signal by capturing the PlGF ligand. There are also studies reporting that PlGF is responsible for resistance to anti-VEGFs in various retinal diseases including diabetic macular edema and AMD. Aflibercept may overcome this resistance by inhibiting PlGF.[34] In our study, we thought that although ranibizumab was effective, drug tolerance could developed and duration of action may be shorter than aflibercept when BRVO pathogenesis was considered.

According to VIBRANT study, rescue IVA implemented in the laser group from week 24 a provided significant visual improvements until week 52.[35] Although the combination of IVA and laser is observed to be beneficial in this study, lack of a comparative study with anti-VEGF agents does not provide complete information about the efficacy.

The efficacy of anti-VEGF treatments on ME caused by BRVO were reported in all of these studies; however, anti-VEGF treatments have serious ocular side effects (i.e. endophthalmitis, increase of IOP, retinal detachment, traumatic cataract, uveitis, central retinal artery occlusion, and vitreous hemorrhage). Therefore, use of anti-VEGF treatments is limited by physicians.[36] For this reason, alternative treatment options such as combination therapy or sole laser therapy have been developed over time.[5, 8-10]

Oxygen consumption of photoreceptors in the outer retina decreases following GLP, leading to oxygen diffusion from the choroid to inner retina; this eventually increases the oxygen permeability and reduces hypoxia. Inner retinal oxygenation causes vasoconstriction, resulting in decreased hydrostatic pressure in the capillaries and venules. As a result, fluid effusion decreases and ME resolves in retinal tissues. As a result, it regresses neovascularization by decreasing the VEGF concentration.[37,38] However, it can be trigger central scotoma by causing macular scars and atrophy.[39] Development of central scotoma was not observed in any patient due to GLP in our study.

In a prospective randomized study conducted by BRVO Study Group, GLP was pointed out to significantly improve long-term visual prognosis of ME caused by BRVO. It was reported in the same study that patients with visual acuity of 20/40 and below significantly benefited from the therapy than the control group.[5]

Several studies have interpreted alterations on SFCT in eyes with BRVO. Chung et al. found that subfoveal choroidal volume in eyes with BRVO was significantly higher compared to the volume of healthy fellow eyes, and reported that it decreased significantly following intravitreal anti-VEGF therapy [40]. On the contrary, Du et al. demonstrated that SFCT was lower in eyes with BRVO than those without BRVO [41]. In a study performed by Kim et al., no difference was found between SFCT values in acute BRVO with ME and fellow healthy eyes. In eyes with acute BRVO, the choroid is thicker in the vascular area involving occlussion, and this situation is directly affected by the severity of ME. And also, they reported that the change in choroidal thickness had no effect on the prognosis in visual acuity. IVR can diminish choroidal thickness but can not return it to normal limits [42]. In our study, SFCT values remained stable in the IVA group, but caused a gradual decrease in the IVR group. We interpreted this situation to evaluation of the molecular structures of drugs and the subfoveal area, not the ischemic region.

Possible reasons blamed for choroidal thickening include damage of the outer blood-retinal barrier and elevated localized VEGF levels. In an experimental study of BRVO, high VEGF mRNA levels were found only in the occlusion area, and VEGF expression was detected to increase in the hypoxic retina close to the area of affected. Moreover, the most important factor determining the level of VEGF

expression was the degree of hypoxia [43]. Increment of local VEGF levels can trigger choroidal dilation and thickening near the hypoxic retina.

Advantages of current study include a single-centered design, longer follow- up period, and homogeneous distribution of groups as well SFCT, CFT, CFV, and consideration of diurnal variation, age, gender, ethnicity. The main limitation of the present study is retrospective design and relatively smaller sample size.

Consequently, both IVA and IVR injections with PRN protocol in combination with GLP have been shown to be more effective treatment options for ME caused by BRVO. Mean injection count was lower, and anatomical recovery could be observed in the final examination in the IVA group. In IVA may be preferred instead of IVR for long-term efficacy when combined with GLP in patients with ME caused by BRVO.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained prior to every surgical procedure from all individual participants included in the study.

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