OPEN AIMJ ORIGINAL ARTICLE

Ophthalmology

Comparative Study Between The Effect Of Intravitreal Injection Of Ranibizumab And Aflibercept On Macular Oedema Secondary To Branch Retinal Vein Occlusion

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Received *for publication December 27, 2021;* ***Accepted*** *May 27, 2022;* ***Published online*** *May 27,2022.*

doi: *10.21608/aimj.2022.113278.1759*

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ABSTRACT

Background: Occlusion of retinal veins is a mutual disorder that affect the retina usually occurs when blood clot obstructs a retinal vein.
Aim of The Work: To compare the effects of Ranibizumab versus Aflibercept intravitreal injections on macular edema (ME) caused by branch retinal vein occlusion (BRVO).
Patients and Methods: This study was carried out on two groups of patients of either sex with an age ranging from 35 to 70 years. Every patient injected 3 loading doses. Ranibizumab dose is 0.5 mg dose vial (0.05 mL). Aflibercept dose is 2 mg dose vial (0.05 mL). Follow up was done 1st day post operation then monthly for 4 months. The eyes were followed for VA, IOP, OCT, FFA and any complications.
Results: Both groups showed a significant reduction in central macular thickness (CMT) as well as an improvement in best-corrected visual acuity (BCVA). As regard CMT, the reduction and improvement in Aflibercept group was 71.6%, while the reduction and improvement in Ranibizumab group was 61.2%. Regarding to BCVA, the improvement in Aflibercept group was 70.8%, while the improvement in Ranibizumab group was 44.4%. The majority of the patients were satisfied from improvement of vision after injections.
Conclusion: Both Ranibizumab and Aflibercept were efficient drugs in resolving ME secondary to BRVO with a superior improvement in VA and CMT in Aflibercept group compared with basal values.

Keywords: *Intravitreal injection; Ranibizumab; Aflibercept; macular edema; branch retinal vein occlusion.*

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.*
Authorship: *All authors have a substantial contribution to the article.*

INTRODUCTION

BRVO is a frequent disorder affecting circulation of the retina that occurs when a thrombus obstructs a retinal vein.[1] After diabetic retinopathy, CRVO and BRVO are the most frequent retinal disease.[2,3]

The prevalence of BRVO is about 4 per 1000 persons compared with CRVO which has a prevalence of about 0.8 per 1000 persons. BRVO frequently happens at arterio-venous crossing sites. pathogenically it follows the Virchow's triad principle (endothelial damage, hypercoagulability, and stasis) and associated with other cardiovascular risk factors.[4,5,6]

The release of inflammatory mediators like TNF-alpha, leukotrienes, integrins, prostaglandins, and vascular endothelial growth factor (VEGF) follows endothelial damage in the affected blood vessels, resulting in an inflammatory response.[7]

As proved, VEGF has a crucial role in the persistence and development of secondary ME.[8] This condition may lead to severe vision loss owing to possible complications including vitreous bleeding, retinal neovascularization, and macular ischemia, but the most frequent cause of diminution of vision is ME.[9]

For many years, the first line of treatment for this ME was grid laser photocoagulation. With the presence of anti-VEGF agents, intravitreal injections of Ranibizumab and Aflibercept have become the first-line therapy methods for ME. As reported in the VIBRANT study, the use of anti-VEGF contributed to a large improvement in visual acuity and a decrease in CMT in eyes with ME secondary to BRVO.[10,11]

PATIENTS AND METHODS

This is a comparative study between two groups of patients, one group injected with Ranibizumab and the other injected with Aflibercept at Al-Azhar university hospitals in Cairo and Mansoura health insurance hospital, in the period from January 2020 to July 2021

Inclusion criteria based on OCT, which CMT ≥ 300 µm, age group 35-70 years old, both genders, pupillary dilatation and participant cooperation

enough to get sufficient fundus pictures and fundus examination. While the exclusion criteria were ocular media opacity, uncooperative patient, fluorescein dye hypersensitivity, macular holes, evidence of retinal surgery and vitro-macular traction or retinal detachment.

Demographic data: age, gender, history of previous intraocular surgery and medication received. Ophthalmic examination**:** Including BCVA using Landlots' broken ring chart then converted to logMAR and slit lamp biomicroscopy was used to assess: corneal clarity, state of iris, pupillary reaction, shape, regularity and lens morphology. Goldman applanation tonometer for the measurement of intraocular pressure.

Fundus examination to detect site of vein occlusion, extent of hemorrhage and any other vascular or disc disorders. FFA and OCT were done for all patients.

Both drugs were injected intravitreal once monthly for 3 months under complete sterile conditions via the pars plana. Prophylactic topical antibiotic moxifloxacin 0.5% one day before and then over week after operation.

Both Ranibizumab (Lucentis) and Aflibercept (Eylea) are preservative-free, colorless sterilized solutions that are packaged in single-use glass vials. The Ranibizumab dose is 0.5 mg (delivers 0.05 mL of 10 mg/mL Ranibizumab) while the dose of Aflibercept is 2 mg (delivers 0.05 mL of 40 mg/mL Aflibercept)**.**

Informed consent was obtained and correct side eye was confirmed.

After sterilization, the surgeon measured a safe distance behind the limbus in the infero-temporal quadrant with a measuring caliper (3.5 mm in the phakic eye while 3 mm in the pseudophakic).

After injection, eye closed with sterile dressing. Moxifloxacin eye drops 4 times/day and brimonidine tartarate 0.15% eye drops twice/day were prescribed for 5 days.

The follow-up was one day after injection and then every month for 4 months.

Statistical analysis: The SPSS software for Windows was used to analyze the data (Standard version 21). The Shapiro test was performed to determine the data's normality. Numbers and percentages were employed to describe qualitative data. For normally distributed data, mean ± SD was employed, whereas for non-normal data, median (min-max) was employed. The following tests were used: Fischer exact test, Student t test, Mann Whitney test and Wilcoxon signed rank test.

The Level of significance for all of the above-mentioned statistical tests is set at 5%.When $p \leq 0.05$, the findings have been deemed significant. The findings are more significant when the p-value is minimal.

RESULTS

Concerning demographic data and medical history among the examined groups, there have been no statistically significant differences between the two groups in terms of all demographic characteristics as well as all medical problems as seen in table (1&2).

Variables	Aflibercept injection group (n=10)	Ranibizumab injection group (n=10)	Test of significance	P value
Age (years)			t=1.67	0.113
Mean ± SD	60.90±11.04	53.80±7.71		
Min-Max	41-75	45-66		
Age classes			FET	0.527
<50 y	2 (20.0%)	4 (40.0%)		
50-60 y	2 (20.0%)	3 (30.0%)		
>60 y	6 (60.0%)	3 (30.0%)		
Gender	8 (80.0%)	8 (80.0%)	-	-
Male	2 (20.0%)	2 (20.0%)		
Female				

t: student t- test, FET: Fischer exact test

No statistically significant differences in all demographic characteristics between the two groups (age, age classes and gender) (P>0.05).

Table 1: Demographic data among studied groups:

Medical history	Aflibercept injection group (n=10)	Ranibizumab injection group (n=10)	P value
Hypertension	5 (50.0%)	6 (60.0%)	0.1
Diabetes	3 (30.0%)	4 (40.0%)	0.1
Hypercholesterolemia	1 (10.0%)	1 (10.0%)	0.1

Fischer exact test was used

No statistically significant differences in medical history between the two groups (hypertension, diabetes, and hypercholesterolemia) (P > 0.05).

Table 2: Medical history among studied groups:

In the context of BCVA, figure (1) showing no significant differences were recorded among both groups either at baseline as well as after 1st, 2nd and 3rd injections. In addition, the change in Aflibercept injection group was 70.8%, while the change in Ranibizumab injection group was 44.4%.

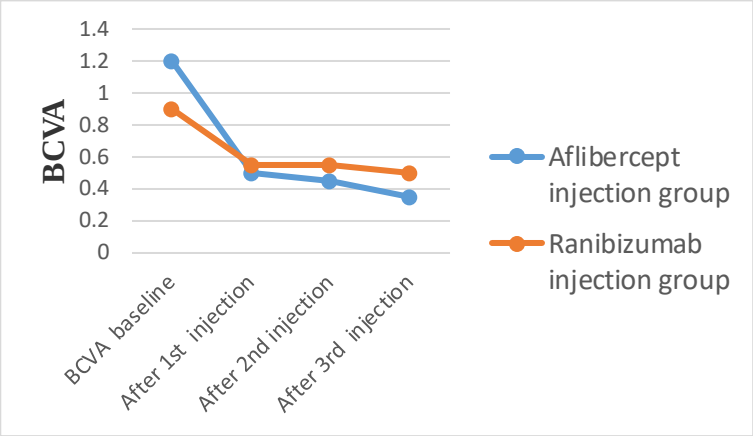

Fig.1: Best corrected visual acuity among studied groups.

No statistically significant differences in BCVA between the two groups at baseline, as well as after 1st, 2nd, and 3rd injections. In addition, the change in Aflibercept injection group was 70.8%, while the change in Ranibizumab injection group was 44.4%.

Additionally, there were statistically significant differences between baseline and all follow-up periods (1st, 2nd, and 3rd injections) as regards BCVA. There have also been statistically significant differences between the three examined follow-up periods and each other's in terms of both Aflibercept and Ranibizumab injection groups as illustrated in tables (3&4).

Best Corrected Visual Acuity	BCVA (Aflibercept injection group)			
	Baseline	After 1st injection	After 2nd injection	After 3rd injection
Median (Min-Max)	1.2 (0.1-1.5)	0.5 (0.1-1.3)	0.45 (0.1-1.0)	0.35 (0.0-1.0)
Wilcoxon signed rank test (P1)	-	Z=2.69 P=0.007*	Z=2.67 P=0.007*	Z=2.81 P=0.005*
Wilcoxon signed rank test (P2)	-	-	Z=2.25 P=0.024*	Z=2.85 P=0.004*
Wilcoxon signed rank test (P3)	-	-	-	Z=2.46 P=0.014*

*significant p ≤0.05
P1: Comparison between baseline and 1st, 2nd, 3rd injections
P2: Comparison between 1st injection and 2nd, 3rd injections
P3: Comparison between 2nd injection 3rd injections
Statistically significant differences among baseline and all follow up periods (1st, 2nd and 3rd injections). There have also been statistically significant differences between the three examined follow-up periods and each other's.

Table 3: Best corrected visual acuity among Aflibercept injection group at different follow up

Best Corrected Visual Acuity	BCVA (Ranibizumab injection group)			
	Baseline	After 1st injection	After 2nd injection	After 3rd injection
Median (Min-Max)	0.9 (0.2-1.5	0.55 (0.1-1.40)	0.55 (0.1-1.50)	0.50 (0.0-1.5)
Wilcoxon signed rank test (P1)	-	Z=2.72 P=0.007*	Z=2.72 P=0.007*	Z=2.81 P=0.005*
Wilcoxon signed rank test (P2)	-	-	Z=0.949 P=0.343	Z=2.53 P=0.011*
Wilcoxon signed rank test (P3)	-	-	-	Z=2.03 P=0.042*

*significant p ≤0.05
P1: Comparison between baseline and 1st, 2nd, 3rd injections
P2: Comparison between 1st injection and 2nd, 3rd injections
P3: Comparison between 2nd injection 3rd injections
Statistically significant differences among baseline and all follow up periods (1st, 2nd, and 3rd injections). There have also been statistically significant differences between the three examined follow-up periods and each other's.

Table 4: Best corrected visual acuity among Ranibizumab injection group at different follow up

Regarding to CMT, no significant differences were recorded among both groups either at baseline as well as after 1st, 2nd and 3rd injections. In addition, the change in Aflibercept injection group was 71.6%, while the change in Ranibizumab injection group was 61.2% as seen in figure (2).

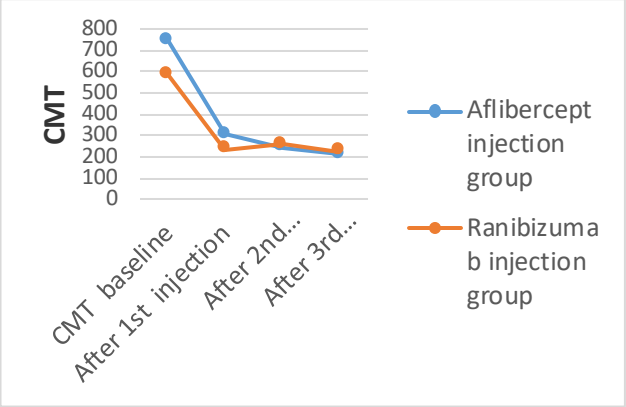

Fig 2: Central macular thickness among studied groups.

No statistically significant differences in CMT between the two groups at baseline as well as after the 1st, 2nd, and 3rd injections (P > 0.05). Moreover, the change in Aflibercept injection group was 71.6%, while the change in Ranibizumab injection group was 61.2%

Additionally, as seen in tables (5&6) there were statistically significant differences among baseline and all follow up periods (1st, 2nd and 3rd injections) as regards CMT (in terms of both Aflibercept and Ranibizumab injection groups), also, statistically significant differences existed between the three follow-up periods examined and each other's in terms of Aflibercept injection group only (but not Ranibizumab)

CMT	CMT (Aflibercept injection group)			
	Baseline	After 1st injection	After 2nd injection	After 3rd injection
Median (Min-Max)	742 (314-1182)	303.5 (191-1032)	246 (168-752)	210.50 (165-648)
Wilcoxon signed rank test (P1)	-	Z=4.65 P=0.001*	Z=6.07 P≤0.001*	Z=6.58 P=0.005*
Wilcoxon signed rank test (P2)	-	-	Z=1.73 P=0.083	Z=2.55 P=0.011*
Wilcoxon signed rank test (P3)	-	-	-	Z=2.56 P=0.01*

Statistically significant differences among baseline and all follow up periods (1st, 2nd and 3rd injections). There have also been statistically significant differences between the three examined follow-up periods and each other's (P<0.05).

Table 5: Central macular thickness among Aflibercept injection group at different follow up:

CMT	CMT (Ranibizumab injection group)			
	Baseline	After 1st injection	After 2nd injection	After 3rd injection
Median (Min-Max)	584 (361-828)	236.5 (113-326)	259 (136-515)	226.50 (166-454)
Wilcoxon signed rank test (P1)	-	Z=6.72 P≤0.001*	Z=6.17 P≤0.001*	Z=6.29 P=0.005*
Wilcoxon signed rank test (P2)	-	-	Z=1.53 P=0.126	Z=0.765 P=0.444
Wilcoxon signed rank test (P3)	-	-	-	Z=1.02 P=0.308

Statistically significant differences among baseline and all follow up periods (1st, 2nd and 3rd injections), while there have been no statistically significant differences between the three examined follow-up periods and each other's.

Table 6: Central macular thickness among Ranibizumab injection at different follow up:

DISCUSSION

Vascular endothelial growth factor has a crucial role in the growth and persistence of ME caused by BRVO.[12]

Ranibizumab, Aflibercept and Bevacizumab are the first-line treatment of ME as anti-VEGF drugs. While other drugs are authorized for this reason, bevacizumab is used off-label. Successful treatment results have been reported in substantial studies that included follow-up and therapy criteria.[13]

At the end of the study, BCVA shows no significant differences were recorded among both groups either at baseline as well as after 1st, 2nd and 3rd injections. In addition, the change in Aflibercept injection group was 70.8%, while the change in Ranibizumab injection group was 44.4%. Additionally, there were statistically significant differences between baseline and all follow-up periods (1st, 2nd, and 3rd injections) as regards BCVA. There have also been statistically significant differences between the three examined follow-up

periods and each other's in terms of both Aflibercept and Ranibizumab injection groups.

These data came in accordance with a study of 259 treatment-naive eyes from 258 patients who received Ranibizumab and Aflibercept or a mixture of the two (n = 83, 97, and 79, respectively) between 2013 and 2018, with a follow-up period of more than 6 months. Hogg and his colleagues demonstrated that, eyes getting Ranibizumab or Aflibercept exhibited indeterminate vision increases at one year 8.0 (5.0-11.0) and 9.6 (7.2-12.1).[14]

In the same line, Ozkaya and his colleagues demonstrated that, mean baseline, month 3, and month 6 BCVA in Ranibizumab group was 0.95±0.61-, 0.50±0.30-, and 0.66±0.58 LogMAR respectively. Mean baseline, month 3 and month 6 BCVA in Aflibercept group was 0.85±0.65-, 0.61±0.58- and 0.65±0.55 LogMAR, respectively, this was evaluated in a retrospective, case-control study in which patients with ME secondary to BRVO were treated with Ranibizumab and Aflibercept and were undergo 6 months follow-up time.[15]

Similarly, to some extent, Hykin and his colleagues have compared the clinical efficacy of Ranibizumab, Aflibercept and Bevacizumab intravitreal injections for ME owing to CRVO. At 100 weeks, the average increase in BCVA letter scores for Ranibizumab was 12.5, 15.1 for Aflibercept, and 9.8 for Bevacizumab.[16]

In the context of CMT, no significant differences were recorded among both groups either at baseline as well as after 1st, 2nd and 3rd injections. In addition, the change in Aflibercept injection group was 71.6%, while the change in Ranibizumab injection group was 61.2%.

In the same line, Ozkaya and his colleagues have demonstrated that, in the context of CMT, the average baseline month 3 as well as month 6 values in the Ranibizumab group were 598±189-, 473±162- and 359±134 µm respectively. While CMT in Aflibercept group average baseline month 3 as well as month 6 was 512±141-, 345±154- and 374±172 µm respectively.[15]

Similarly, Spooner and his colleagues demonstrated in their meta-analysis study, which was conducted on a whole of 1236 eyes from 22 investigations, which the average baseline CMT varied from 406.0 to 681.0 µm with an overall mean improvement in CMT decrease of 228 µm.[17]

However, Kaldırım and Yazgan demonstrated that (Ranibizumab, Aflibercept, and Bevacizumab) were more efficient in maintaining the reduced CMT towards the conclusion of the sixth month therapy.[18]

All BRVOs with ME have a trace of macular ischemia despite the fact that it might not be broad enough to be classified as an 'ischemic BRVO'.[19] Ischemic events that occur with other factors producing photoreceptor and retinal damage will result in a non-adjustable limitation in visual acuity, regardless of the existence or lack of ME.[20] This explains why some patients treated with Ranibizumab or Aflibercept have had doubtful visual results.[14]

CONCLUSION

Ranibizumab and Aflibercept are effective drugs as anti-VEGF in terms of the treatment of ME secondary to BRVO with comparable efficiency. Additionally, they were related to a significant improvement in BCVA as well as a significant reduction in CMT compared with the basal values in each group. Despite the promising outcomes in the current study, small number of patients per group is considered the main limitation of our study.

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