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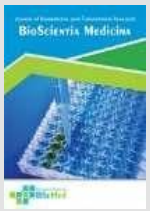

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Comparing the Optical Coherence Tomography Outcomes of Intravitreal Injection Anti Vascular Endothelial Growth Factor in Branch Retinal Vein Occlusion (BRVO)

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A B S T R A C T

Background: BRVO is a blockage of the branches of the retinal vein due to a thrombus. The prevalence of 10-year BRVO is 1.6 per 100 subjects. The effect of anti-VEGF injection on BRVO management is effective in improving visual acuity and reducing macular oedema. **Case presentation:** A man, 32 years old, presented to the ophthalmology clinic at the Dr. M. Djamil General Hospital with a chief complaint of blurred vision in his left eye 1 week before admission. The blurred vision began suddenly. Visual acuity in LE was 20/50 and did not advance with a pinhole. Funduscopic examination of LE showed clear media, rounded papillae with well-defined borders, blood vessels aa:vv = 1:3, venous tortuosity (+) increased in the inferotemporal quadrant; retina: Bleeding (+) with dot blot and flame-shaped inferiorly, exudate (+) cotton wool spots at the inferotemporal region; foveal reflex (+)↓ on the macula. OCT LE examination showed macular intraretinal hypo-reflection and macular thickening with a central macular thickness of 617 µm. The physical examination showed a body weight of 114.9 kg, a height of 173 cm, and a body mass index of 38.4. Within 5 months after 3 times administrations of intravitreal injections of anti-VEGF bevacizumab and ranibizumab, visual acuity of LE: 20/25 was obtained, and increased appearance of the retinal fundus and OCT LE. **Conclusion:** Intravitreal injection therapy of anti-VEGF bevacizumab and ranibizumab is effective in reducing macular oedema and restoring visual acuity in BRVO.

1. Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder after diabetic retinopathy and is often associated with visual loss.[1] RVO is a disorder of the retinal venous system caused by thrombus formation, which can affect the central part, hemi-central, or branch parts of the retinal vein. Multifactorial pathogenesis and pathophysiology of RVO disease are yet known for certain. RVO is classified as CRVO (central retinal vein occlusion), BRVO (branch retinal vein occlusion), and HRVO (hemicentral retinal vein occlusion) based on the location of the blockage. CRVO occurs when there is an obstruction that affects central venous vessels, BRVO occurs when there is obstruction of the blood vessel branches in the retinal vein, and HRVO occurs when the obstruction occurs in the superior central vein or inferior central vein. RVO has ischemic and non-ischemic forms.[1,2]

The Beijing Eye Study reported a 10-year incidence of BRVO was 1.6 per 100 subjects.[3] BRVO prevalence ranged from 0.7% in patients aged <60 years, 1.2% in 60-69 years, 2.1% in patients aged 70 -79 years, and increased to 4.6% at the age of over 80 years.[1] Based on a study by Harhiu et al., BRVO generally occurs in elderly patients. However, it can also occur in patients aged less than 49 years who have high-risk factors such as atherosclerosis, cardiovascular disease,

dyslipidemia, diabetes mellitus, hypertension, and increased body mass index at the age of 20 years.[4] The pathophysiology of BRVO is not well understood, but in most cases, venous compression is found at the arteriovenous (A/V) intersection of the retina. The consequences of compression on the retinal vein include blood flow turbulence, endothelial damage, and thrombosis, which in turn causes occlusion of the retinal vein branches. Hypoxia that occurs due to blockage of blood flow can trigger an increase in the production of vascular endothelial growth factor (VEGF), which will then increase vascular permeability. This is the most common cause of macular edema and neovascularization in BRVO.[5,6] Symptoms that are often experienced by patients with BRVO include decreased visual acuity and vision, which is sometimes blurred without being accompanied by pain in one eye caused by the appearance of macular oedema, macular ischemia, or neovascularization.[7] The main goal of BRVO management is to maintain good visual acuity thus, it does not decrease progressively and to prevent complications. Several previous studies have shown the effect of anti-VEGF injections on BRVO management. This therapy is effective in increasing visual acuity and reducing macular oedema.[7,8]

2. Case Presentation

A male patient, aged 32 years, presented to the ophthalmology clinic of Dr. M. Djamil General Hospital Padang on May 28th, 2020, with a chief complaint of blurred vision in the left eye that was felt since ± one week before admission. The blurred vision began suddenly. There was no black spot vision, and the patient did not see flashes of light. There was no history of using glasses. There was no history of previous eye surgery. There was no history of trauma, hypertension, diabetes mellitus, or dyslipidemia. There was no family history of vision loss. The physical examination of the patient showed a blood pressure of 130/80 mmHg, a heart rate of 96 times/minute, a respiratory rate of 20 times/minute, a body weight of 114.9 kg, a height of 173 cm, and a body mass index of 38.4.

Results of an ophthalmological examination of the left eye showed visual acuity of the left eye at 20/50 and did not progress with the pinhole. There were no abnormalities in the cornea, anterior segment, iris, pupil or lens, while the visual acuity of the right eye was 20/20. Fundoscopic examination results of the right eye showed clear media, rounded papillae with firm boundaries, blood vessels aa:vv = 2:3, retina: bleeding (-), exudate (-), with Rf fovea (+), IOP: 11mmHg; whilst the funduscopy of the left eye showed clear media, rounded papillae with well-defined borders, blood vessels aa:vv = 1:3, venous tortuosity (+) increased in the inferotemporal quadrant, retina: bleeding (+) dot blot and flame-shaped inferiorly, exudate (+) cotton wool spots at the inferotemporal region, macula showed Rf fovea (+)↓, IOP: 12mmHg. OCT examination results of the left eye showed macular intraretinal hypo-reflection and macular thickening with a central macular thickness of 617 µm, and OCT of the right eye showed a central macular thickness of 246 µm.

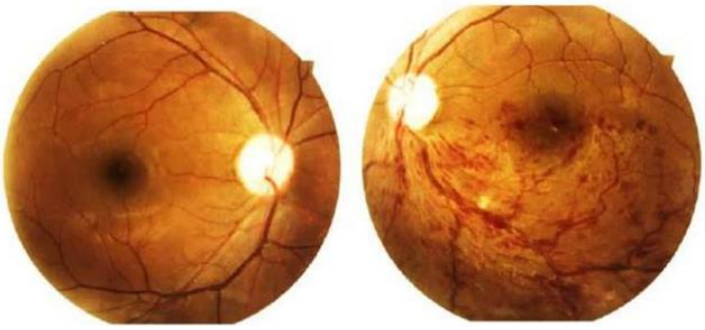


Figure 1. Fundus photographs of the right eye (left image) and left eye (right image).

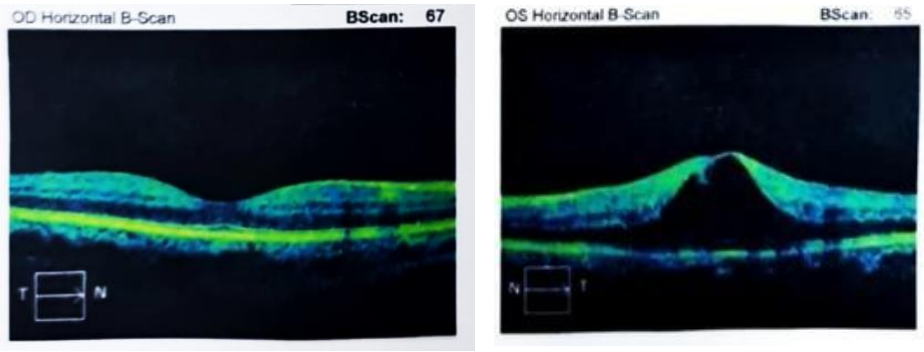


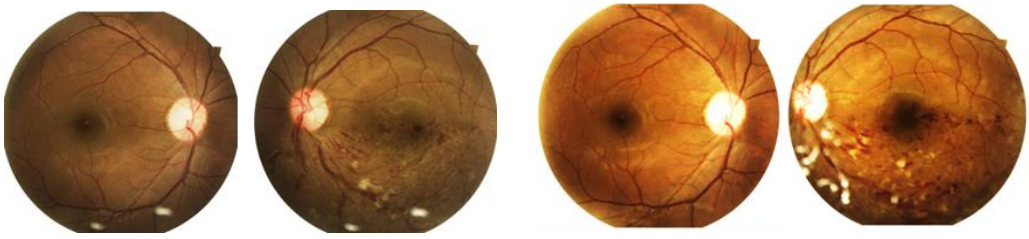
Figure 2. OCT photographs of the right eye (left image) and left eye (right image).

Laboratory results showed a fasting blood glucose level of 82 mg/dl, a two-hour postprandial glucose level of 120 mg/dl, total cholesterol of 180 mg/dL, a triglycerides level of 96 mg/dL, HDL level of 51 mg/dL, and LDL of 110 mg/dL.

This patient was diagnosed with branch retinal vein occlusion OS with Macular Edema. The patient was consulted by the department of internal medicine to control his cholesterol and reduce his BMI. The patient was given Bevacizumab 1.25 mg intravitreal injection in the left eye.

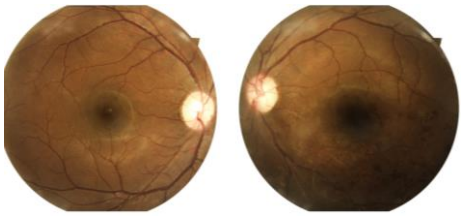
Table 1. Development of the patient's vision of the left eye during his treatment.

Date	OS vision	Macular thickness of OS
28-05-2020	20/50	617 µm
03-06-2020	20/25	282 µm
27-07-2020	20/40	579 µm
04-08-2020	20/25	263 µm
06-10-2020	20/100	556 µm
20-10-2020	20/25	263 µm



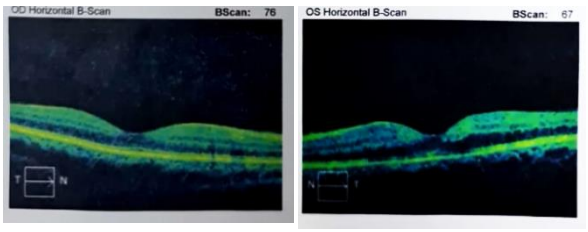
1 week post first injection (3rd June 2020)

2 months post first injection (29th July 2020)

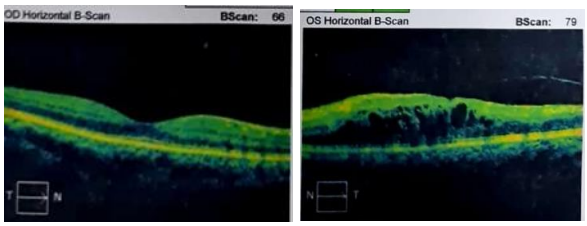


2 weeks post third injection (20th October 2020)

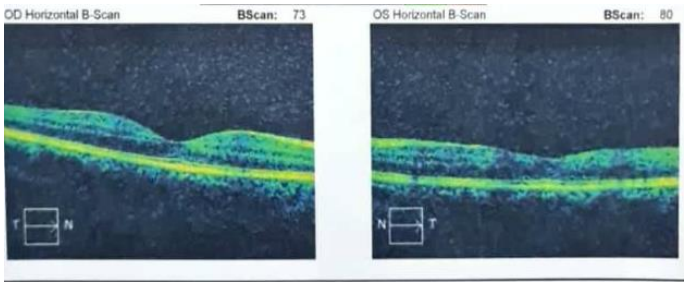
Figure 3. Development of the fundus photos of the right and left eyes during treatment.



1-week post first injection (3rd June 2020)



2 months post first injection (29th July 2020)



2 weeks post third injection (20th October 2020)

Figure 4. OCT examination progress.

3. Discussion

BRVO is an occlusion of the branches of the retinal vein. Histopathologically, at the intersection of the arteriovenous, retinal arteries and veins have the same tunica adventitia and, in some cases, can extend to the tunica media. The lumen of the vein can be compressed by up to 33% in the crossing area. Arterial wall thickening compresses the vein and causes flow turbulence, endothelial cell damage, and thrombus occlusion. Venous obstruction results in increased venous pressure, which exacerbates drainage capacity and then causes dilated veins and increased tortuosity, which can lead to rupture of the vessel wall with intraretinal bleeding and cause edema and macular ischemia, whose mechanisms are yet well understood. Vision loss is usually associated with macular ischemia, macular edema, or complications of neovascular disease. Retinal ischemia is the most important factor for vascular endothelial growth factor (VEGF) expression.[9,10,11]

Common risk factors that underlie BRVO include age > 50 years, hypertension, hyperlipidemia, diabetes mellitus, smoking, cardiovascular disease, and an increase in body mass index at the age of 20 years.[7,11] In this case report, the patient was 32 years old but had a body mass index risk factor of 38.4, and the risk of increased blood lipid levels was proven by the results of a total blood cholesterol examination of 180 mg/dl. Although it still had not reached the upper limit, it was almost close. Based on The Beijing Eye Study, obesity and hyperlipidemia are involved in the pathogenesis of arteriosclerosis. Thus, it can give rise to various diseases that arise due to stiffness and blockage of blood vessels, one of which is BRVO.[3,12]

In this case, the patient came with a chief complaint of blurred vision in the left eye and without pain. The blurry vision felt suddenly since about one week before admission. In rare cases, patients with BRVO may present with floaters from a vitreous haemorrhage if the initial venous occlusion is not recognized and retinal neovascularization has occurred. BRVO is divided into ischemic and nonischemic types. Specifically, if the perfusion occlusion (non-ischemic) shows little intraretinal bleeding and in non-perfusion (ischemic), the bleeding is more. The Branch Vein Occlusion Study Group defines ischemic BRVO as a non-perfused area larger than five disc diameters on angiography. If the

occlusion occurs in the peripheral veins of the macular veins, there may be no macular involvement and no decreased visual acuity.[13,14]

On funduscopic examination of BRVO patients, flame-shaped haemorrhage, macular oedema, and often cotton wool spots (nerve fibre layer infarction) can be found in the retinal area, which is supplied by the affected vein.[7] The results of the funduscopic examination in this patient's right eye were within normal limits. The left eye had a ratio aa:vv 1:3, venous tortuosity (+) increased in the inferotemporal quadrant, with bleeding (+) dot blot and flame-shaped inferiorly, exudate (+) inferotemporal cotton wool spots, decreased foveal reflex (+). Figure 5 shows a branch retinal vein occlusion of an inferotemporal branch vein. Fundus radiograph shows extensive haemorrhage and cotton wool spots at the base of the venous occlusion.[5,10,15]

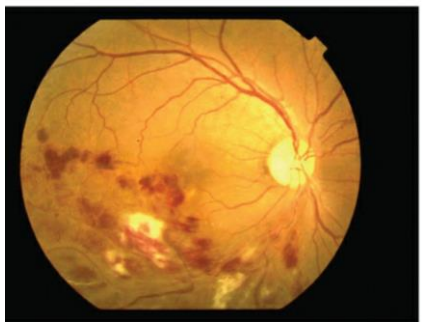


Figure 5. BRVO in the inferotemporal quadrant.[5]

BRVO patients present with a funduscopic appearance of intraretinal bleeding that is profuse and increasingly extensive from a week to a month. This indicates that the previous partial occlusion has become a total occlusion. Over time, intraretinal haemorrhage can be completely absorbed. Without the characteristic intraretinal segmental haemorrhage, the diagnosis may be more difficult in this BRVO, but the segmental abnormal vascular distribution that occurs during the acute phase may persist. In the chronic phase, after intraretinal haemorrhage has been absorbed, the diagnosis of BRVO depends on detecting an abnormal vascular distribution, including capillary non-perfusion, capillary dilatation, microaneurysms, vessel telangiectasia, and collateral vessel formation.[16,17]

Optical coherence tomography (OCT) is the most important imaging modality in the treatment of patients with BRVO and macular oedema. OCT can be used to monitor the success of treatment in macular oedema. In accordance with Figure 6, OCT findings in BRVO patients can include cystoid macular oedema, intraretinal hyperreflectivity from bleeding, and sometimes subretinal fluid. On the OCT examination at the patient's initial arrival, a central macular thickness of 617 µm was found, where normally the central macular thickness is not more than 252 µm and intraretinal hypo-reflectivity was seen, indicating macular oedema.[5,16,18]

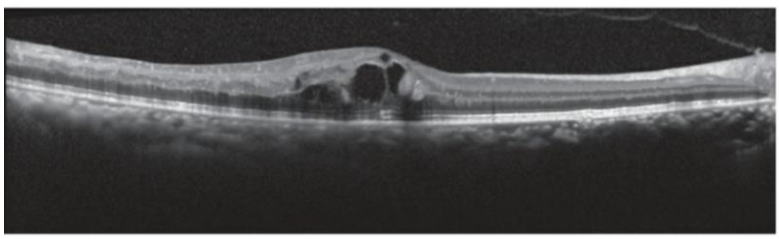


Figure 6. OCT view of BRVO patients.[5]

Complications that affect visual acuity in BRVO patients include macular oedema, macular ischemia, and neovascularization. The Branch Vein Occlusion Study Group reported that 31-41% of patients with ischemic BRVO developed neovascularization and vitreous haemorrhage, compared with only 11% for non-ischemic BRVO.[16,17]

Macular oedema in BRVO is characterized by the accumulation of fluid in the deep retinal layer, which, when the condition gets worse, often forms cystic spaces up to the subretinal fluid. Macular oedema has a complex pathophysiology. Increased hydrostatic pressure causes damage to the tight junctions of the capillary endothelium, resulting in leakage of fluid and vascular protein. The hypoxia that occurs stimulates an increase in VEGF, which contributes to damage to the blood-retinal barrier. This situation triggers accumulation in the macula.[16,17] Thus that VEGF inhibition is a treatment for macular oedema in BRVO.[8,9] Several previous studies have studied the effects of intravitreal injection. There are several anti-VEGF agents that can be used in BRVO, such as ranibizumab (Lucentis), bevacizumab (Avastin), pegaptanib (Macugen), and aflibercept (Eylea).[19,20]

In this case report, intravitreal injections of bevacizumab (Avastin) were performed in the patient's left eye. There have been many prospective studies and several case series to evaluate bevacizumab in the treatment of BRVO macular oedema. Most studies show that bevacizumab is effective in improving visual acuity and reducing macular oedema as measured by OCT. The study by Rush et al. and Vader et al. showed that the administration of bevacizumab as therapy is a safe and effective way to reduce macular oedema and improve visual acuity, but the main drawback of bevacizumab therapy is that it requires repeated injections to maintain vision improvement. In accordance with this case, there was recurrent macular oedema in a 2-month follow-up, thus, repeated injections of anti-VEGF were needed.[19,20]

Several studies have shown that there is an effect of bevacizumab on macular thickness in RVO patients with macular oedema. The results of Rahmadani et al.'s study are in line with the study of S.A Mehany et al. (2010), who reported a mean macular thickness of 455 μm±126 decreased to 356 μm±118 after one-month follow-up ($P<0.02$). This study is in accordance with the literature, which states that macular oedema occurs due to abnormal production of VEGF, which can increase retinal capillary permeability and fluid leakage into the extracellular space.[15,16,17]

After two weeks, post-injection follow-up was carried out in this patient clinically. The patient felt the vision in the left eye became clearer, with improvement in left eye vision to 20/25, and did not progress with a pinhole. An OCT examination showed macular edema was significantly reduced, and the central macular thickness was close to normal, i.e. 282 μm.[16,17,18]

In this case report, during a follow-up two months after the intravitreal bevacizumab injections, the patient felt the vision in the left eye become more blurred, with worsening left eye vision to 20/40, did not progress with a pinhole, and right eye vision was 20/20. On funduscopic examination, a flame-shaped OS retina was seen inferiorly (+) and soft exudate inferiorly (+). OCT examination showed a recurrence of cystoid oedema with a central macular thickness of 579 μm. This is in accordance with previous studies that macular oedema in BRVO can recur. Thus, this patient was switched from anti-VEGF to ranibizumab and followed up.[17,18] According to Bartelmann et al.'s study, ranibizumab intravitreal injection compared to bevacizumab, both can manage macular oedema, and even after a total of 17 injections of anti-VEGF and 2.5 years of therapy, no macular oedema was seen, and thus, anti-VEGF therapy was quite effective.[18,19,20] A study conducted by Vader et al., which examined the effectiveness comparison of bevacizumab and ranibizumab in BRVO patients, concluded that based on the change in visual acuity, bevacizumab was not inferior compared to ranibizumab for these patients with BRVO-induced macular oedema within a six-month treatment period. In addition, the anatomical and safety results did not differ between the two.[20]

In this case report, one week after the ranibizumab injection, a follow-up was carried out, with subjective results from the patient who felt the vision in the left eye was getting better with the left eye vision of 20/25 and did not progress with the pinhole. On OCT examination, there was reduced cystoid oedema with a central macular thickness of 263 µm. This indicated that ranibizumab injection was effective against BRVO with macular oedema. However, 2 months after the ranibizumab injection, the patient felt that his vision had become more blurred with 20/100 left eye vision, and on the OCT examination, macular oedema appeared with a central macular thickness of 556 µm. According to Karagiannis et al., recurrent macular oedema in BRVO is associated with a duration of action of ranibizumab which is only ± 4 weeks. Thus, BRVO patients with macular oedema require repeated intravitreal injections of ranibizumab.[14,20,21] Recurrent or persistent macular oedema is a difficult clinical problem and is frequently encountered during BRVO treatment. Until now, there has been no report on how to predict the rate of recurrence of macular oedema after intravitreal injection of anti-VEGF based on the course of the disease in BRVO. Macular oedema is caused by many factors, including not only VEGF but also other inflammatory factors. Thus, some patients may be refractory to anti-VEGF treatment.[17,18]

4. Conclusion

Branch retinal vein occlusion (BRVO) is often accompanied by systemic vascular disease as a risk factor. In this case report, dyslipidemia and obesity were found as risk factors. In the patient, there was a decrease in left eye vision to 20/40, and funduscopic examination showed superficial bleeding, increased venous tortuosity, dot blot bleeding, flame-shaped, and cotton wool spot exudate. BRVO visual acuity reduction is usually associated with macular ischemia, macular oedema, or neovascular complications. In this BRVO case, treatment was carried out with intravitreal injections of anti-VEGF bevacizumab and ranibizumab and obtained effective results in reducing macular oedema and restoring visual acuity.

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