DOI: 10.14744/eer.2022.22931
Eur Eye Res 2022;2(2):69–74

EUROPEAN EYE RESEARCH

ORIGINAL ARTICLE

# Comparison of intravitreal bevacizumab responses in different morphologies of macular edema due to branch retinal vein occlusion: Short-term results

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## Abstract

**Purpose:** The purpose of the study was to compare the results of intravitreal bevacizumab in patients with macular edema (ME) due to branch retinal vein occlusion (BRVO) according to different ME morphologies.

**Methods:** In this retrospective study, 24, 13, and 22 patients with ME type due BRVO were included in the serous retinal detachment group, cystoid ME group, and diffuse ME group, respectively. The best-corrected visual acuity (BCVA) was evaluated with an ETDRS chart, and central macular thickness (CMT) was evaluated by spectral domain optical coherence tomography at the 1st, 2nd, and 3rd months.

**Results:** The mean ages of the patients were 64.25±7.80, 64.84±7.96, and 61.81±6.67 years in the serous, cystoid, and diffuse groups, respectively (p=0.414). While no significant difference was observed in the serous group in terms of BCVA and CMT at the 1st month after injection compared with that in the cystoid group (p=0.201 and p=0.986), BCVA and CMT values at the 2nd and 3rd months were statistically different (p=0.021, p=0.003, p=0.015, and p=0.006, respectively). When the serous group and the diffuse group were compared, only a significant difference was found in CMT at the 2nd month (p=0.016).

**Conclusion:** Intravitreal bevacizumab treatment was more effective in terms of anatomical and visual results in the serous group compared with that in the cystoid group; however, at the end of the 3rd month, it showed similar results with the diffuse group.

**Keywords:** Bevacizumab; cystoid; diffuse; macula; serous retinal detachment.

The most common vascular disease of the retina after diabetic retinopathy is branch retinal vein occlusion (BRVO).[1] The most common cause of vision loss in patients with BRVO is macular edema (ME).[2] Increased intravascular pressure and decreased blood flow in the macular capillaries due to BRVO cause dysfunction of the endothelial blood–retinal barrier and increased vascular permeability, resulting in ME.[3] In addition, similar to other vascular diseases, retinal ischemia caused by vascular occlusion increases the release of inflammatory substances, such as

**Cite this article as:** Vural E, Hazar L, Sirakaya E. Comparison of intravitreal bevacizumab responses in different morphologies of macular edema due to branch retinal vein occlusion: Short-term results. Eur Eye Res 2022;2:69-74.

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**Submitted Date:** 29.11.2021 **Accepted Date:** 09.03.2022

vascular endothelial growth factor (VEGF), and these mediators contribute to edema. Therefore, for treatment, anti-VEGF agents and steroids are used.[4]

Optical coherence tomography (OCT) studies have shown that the types of ME secondary to BRVO are cystoid ME (CME), serous retinal detachment (SRD), and inner retinal thickening (Diffuse).[5,6] Although CME is the most common type of ME secondary to BRVO, SRD and CME often coexist in these patients when examined by OCT.[7,8] SRD is found at varying rates at 15–80% in patients with BRVO.[5,6] The effect of SRD on retinal sensitivity in patients with BRVO with ME remains unclear. Studies have found different effects of SRD on anatomical and functional outcomes after intravitreal injections.[9,10]

This study aims to compare the anatomical and functional results in cases of ME secondary to BRVO, according to ME types (SRD, CME, and diffuse ME [DME]), after intravitreal bevacizumab.

## Materials and Methods

The study is in a retrospective design. The study included 59 patients who were followed up in our retina unit and received three doses of intravitreal bevacizumab treatment for ME due to newly diagnosed BRVO between March 2019 and October 2020. The study was performed in accordance with the Declaration of Helsinki, and local ethics committee approval was obtained.

The diagnosis was made by fundus fluorescein angiography (FFA) (VISUCAM NM/FA; Carl Zeiss Meditec AG, Dublin, CA, USA) and spectral domain OCT (SD-OCT, Heidelberg Engineering, Heidelberg, Germany) after a detailed ophthalmological examination. ME was defined as a central macular thickness (CMT) of 300 µm or larger according to OCT results. Regarding SD-OCT data, ME was classified into three types: DME, CME, and serous DME.

DME was defined by spongy retinal swelling of the macula with reduced intraretinal reflectivity. The type of CME was defined by low reflective intraretinal cystoid spaces and highly reflective septa separating cystoid-like spaces in the macular area. The type of serous ME was defined as a shallow elevation in the retina and an optically open space (hyporeflective area) between the retina and the retinal pigment epithelium. Since these ME types can coexist, if CME and DME types are accompanied by remarkable SRD, they are classified as SRD; otherwise, they are classified as CME or DME according to the findings. However, in the patients in the SRD group, all of them had CME. Patients with non-ischemic BRVO were included in the study. Each BRVO case with a non-perfused area <5 disc diameters according to fundus FA was defined as non-ischemic BRVO. Patients with dense media opacities and glaucoma; cataracts affecting best-corrected visual acuity (BCVA); epiretinal membrane; vitreomacular traction; optic nerve diseases or any uveitis; retinal surgery; non-RVDT causes of ME; and diabetic retinopathy; and those with a history of age-related macular degeneration and central serous chorioretinopathy were not included in the study. Patients previously treated with laser photocoagulation or any intravitreal application were also excluded from the study.

Demographic data of the patients were recorded. The records were scanned retrospectively. At baseline and follow-up visits, all patients had complete ophthalmologic examinations, including BCVA (with ETDRS chart), slit-lamp microscopy, applanation tonometry, fundus biomicroscopy and CMT (with SD-OCT), and FA for ischemic-non-ischemic differentiation. Pre- and post-injection BCVA and CMT values of the patients at the 1st, 2nd, and 3rd months were recorded.

### Statistical Analysis

All analyses were performed with the Statistical Package for the Social Sciences for Windows 21.0 program. Descriptive statistics were used in the analysis of demographic data. Comparisons of mean BCVA and CMT values according to time in a single group were made with the repeated measure analysis of variance (ANOVA) test. Similarly, treatment results of three different subgroups were performed with a one-way ANOVA *post hoc* Bonferroni test. Results were expressed as mean±SD. P<0.05 was considered statistically significant.

## Results

A total of 59 patients – 24 from the serous group, 13 from the cystoid group, and 22 from the diffuse group – were included in the study. Gender distribution (female/male) was 12/12, 5/8, and 12/10 in the serous, cystoid, and diffuse groups, respectively. The mean ages of the patients in the serous, cystoid, and diffuse groups were 64.25±7.80 years, 64.84±7.96 years, and 61.81±6.67 years, respectively (p=0.414).

BCVA and CMT changes according to the months were significant in all three groups (p<0.001, all). BCVA and CMT values of the groups according to the months are given in Table 1, and the graphs of the changes according to the months are shown in Figures 1 and 2. No difference was found between the three groups in terms of pre-injection BCVA (p=0.501) and CMT (p=0.284). When the serous and

**Table 1.** Mean and comparison of BCVA (ETDRS chart) and CMT (μm) values between groups according to time

| Groups | Serous (n=24) | Cystoid (n=13) | Diffuse (n=22) | Serous-cystoid | Serous-diffuse | Cystoid-diffuse |
|---|---|---|---|---|---|---|
| BCVA | | | | | | |
| Before injection | 49 ±6.50 | 47.53±4.73 | 46.50±8.87 | 0.826 | 0.471 | 0.911 |
| 1st month after injection | 58±7.25 | 53.23±8.08 | 54.54±8.63 | 0.201 | 0.314 | 0.885 |
| 2nd month after injection | 60.45±6.15 | 53.30±6.84 | 55.13±9.05 | 0.021* | 0.051 | 0.767 |
| 3th month after injection | 63.58±6.69 | 54.38±5.88 | 59.18±9.25 | 0.003* | 0.132 | 0.178 |
| CMT | | | | | | |
| Before injection | 526.16±100.38 | 474.76±119.17 | 489.27±94.96 | 0.322 | 0.449 | 0.914 |
| 1st month after injection | 382.95±97.87 | 387.92±112.49 | 377.59±64.07 | 0.986 | 0.978 | 0.943 |
| 2nd month after injection | 329.50±55.28 | 396.07±102.20 | 385.77±50.68 | 0.015* | 0.016* | 0.898 |
| 3th month after injection | 296±52.34 | 360.38±82.02 | 335.18±46.64 | 0.006* | 0.067 | 0.436 |

Data were given as Mean±SD (standard deviation). One-way analysis of variance *post hoc* Bonferroni. *P<0.05 was considered statistically significant. BCVA: Best-corrected visual acuity; CMT: Central macular thickness.

**Table 2.** Comparison of BCVA and CMT values between groups according to time

| Groups | Serous-cystoid | Serous-diffuse | Cystoid-diffuse |
|---|---|---|---|
| BCVA | | | |
| Before injection | 0.826 | 0.471 | 0.911 |
| 1st month after injection | 0.201 | 0.314 | 0.885 |
| 2nd month after injection | 0.021* | 0.051 | 0.767 |
| 3th month after injection | 0.003* | 0.132 | 0.178 |
| CMT | | | |
| Before injection | 0.322 | 0.449 | 0.914 |
| 1st month after injection | 0.986 | 0.978 | 0.943 |
| 2nd month after injection | 0.015* | 0.016* | 0.898 |
| 3th month after injection | 0.006* | 0.067 | 0.436 |

One-way analysis of variance *post hoc* Bonferroni. *P<0.05 was considered statistically significant. BCVA: Best-corrected visual acuity; CMT: Central macular thickness.

cystoid groups were compared, BCVA and CMT values at the 2nd and 3rd months were statistically different (Table 2). Follow-up OCT images of a case sample from each group are given in Figure 3.

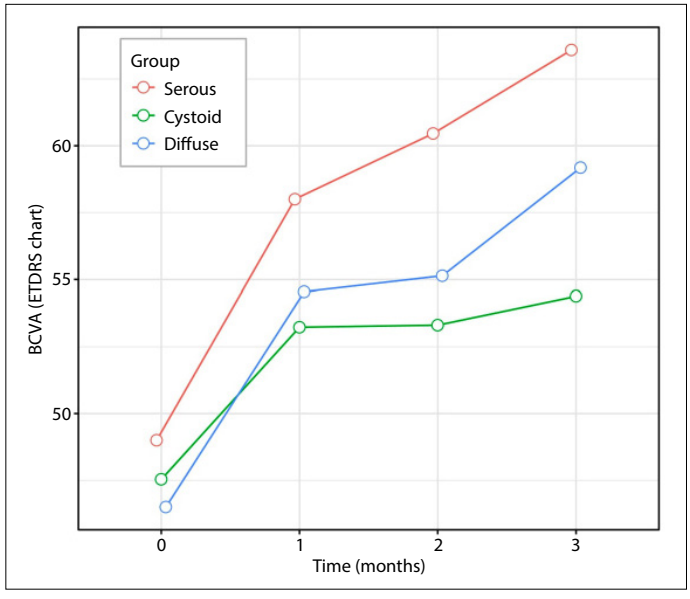


**Fig. 1.** Graph of the change in best-corrected visual acuity in groups over time.

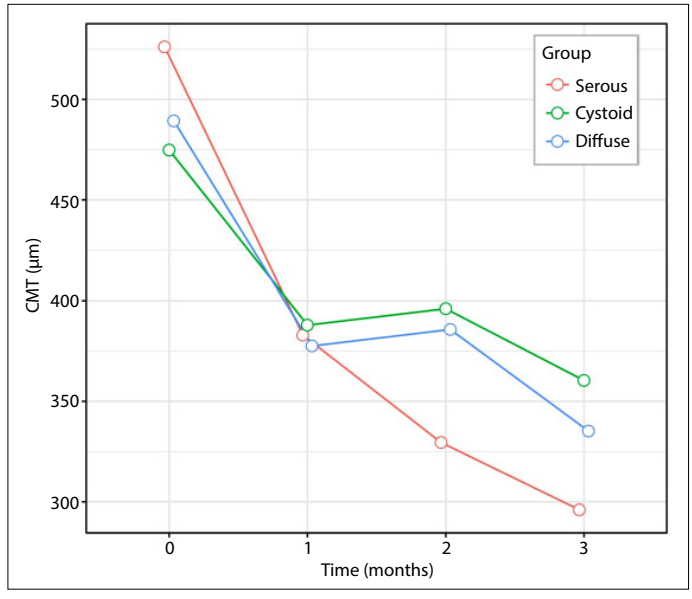


**Fig. 2.** Graph of the change in central macular thickness over time in groups.

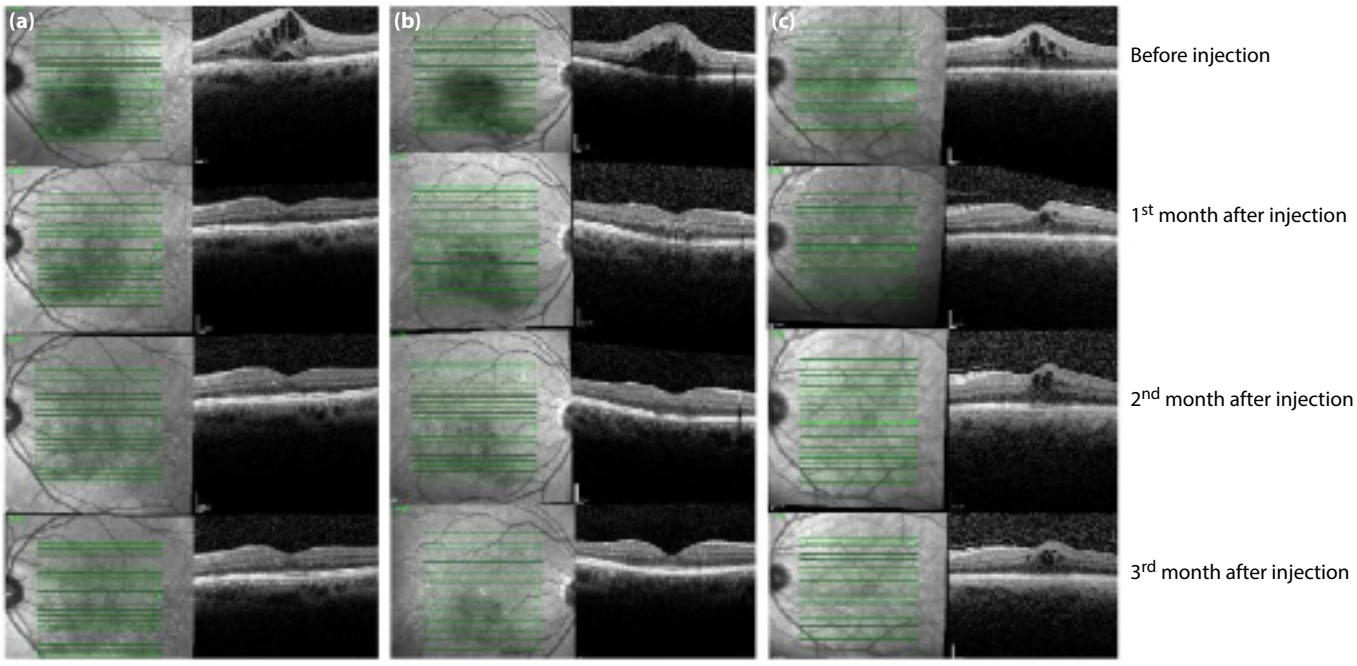


**Fig. 3.** **(a)** Optical coherence tomography (OCT) images before injection (visual acuity [VA]: 47 central macular thickness [CMT]: 600 µm) and at the 1st month (VA: 64 CMT: 319 µm), 2nd month (VA: 60 CMT: 291 µm), and 3rd month (VA: 58 CMT: 288 µm) after injection in a patient with serous retinal detachment, **(b)** OCT images before injection (VA: 50 CMT: 537 µm) and at the 1st month (VA: 62 CMT: 355 µm), 2nd month (VA: 64 CMT: 342 µm), and 3rd month (VA: 67 CMT: 296 µm) after injection in a patient with diffuse macular edema (ME), **(c)** OCT images before injection (VA: 51 CMT: 545 µm) and at the 1st month (VA: 55 CMT: 486 µm), 2nd month (VA: 54 CMT: 454 µm), and 3rd month (VA: 56 CMT: 396 µm) after injection in a patient with cystoid ME.

When the serous group and the diffuse group were compared, there was a difference in CMT only at the 2nd month (Table 2). No difference in time was found between the cystoid and diffuse groups in terms of both BCVA and CMT (Table 2). No correlation was observed between age and changes in BCVA (p=0.839, r=–0.027) and CMT (p=0.730, r=0.046) at 1, 2, and 3 months. At the end of the 3rd month, the rate of increase of 10 letters or more was 87.5% (21/24), 23% (3/13), and 72.7% (16/22) in the serous, cystoid, and diffuse groups, respectively.

## Discussion

In this study, we investigated the prognostic value of BCVA and CMT according to ME types after a three-dose loading intravitreal injection of bevacizumab in patients with ME due to BRVO. In our study, while intravitreal bevacizumab was more effective in the serous ME group – both functionally and anatomically – than the cystoid group at the 2nd and 3rd month, no difference was found at all times with the diffuse group except 2nd month in terms of CMT.

ME is the leading cause of visual impairment in BRVO and may be associated with various morphological changes.[11] The application of OCT imaging has enabled the qualitative analysis of different retinal layers.[11] The morphological variety of retinal changes associated with ME includes diffuse retinal edema, cystic changes, and SRD.[8] CME is typically caused by leakage from retinal vessels and intraretinal cystoid spaces, which are observed in retinal thickening and oval hyporeflective areas on OCT. In SRD, fluid accumulates between the neurosensory retina and the RPE, which is seen as hyporeflective spaces on OCT.[8,11] In the study of Celik et al.,[12] 21 (34%) of 61 eyes with ME secondary to BRVO exhibit edema with accompanying SRD, and all patients with SRD have CME. Eyes with SRD have high foveal thickness with CME. In addition, the SRD group had a significantly lower mean BCVA compared with the CME group. In our study, all cases with SRD were accompanied by CME, and the initial visual acuity was better than that in the DME and CME groups; however, the result was not statistically different from the other groups. Furthermore, the thickest CMT was in the serous group in our study.

Although SRD is a common finding on OCT images, data regarding the effect of SRD on BCVA, CMT, and response to treatments in patients with BRVO are lacking. Park et al.[13] showed that the levels of VEGF in aqueous fluid are higher in patients with BRVO with SRD than in those without SRD. Likewise, Noma et al.[14] found that vitreous fluid levels of

VEGF and soluble intercellular adhesion molecule-1 are higher in patients with RVDT with SRD compared with those with CME. They also reported that BCVA in the SRD group is significantly worse than that in the CME group, and CMB is significantly high in the SRD group. This finding supports the statement that anti-VEGF agents may be more effective in patients with SRD than in those with other types of edema. Although SRD was reported as a poor visual prognosis in Noma et al. study, in our study, we obtained similar visual results with the diffuse group and even better visual results than those in the cystoid group. VEGF inhibitors have a favorable safety profile and are widely used in the treatment of ME secondary to BRVO.[15–17] Celik et al.[12] reported that BCVA and CMB are improved by intravitreal injection of ranibizumab in patients with BRVO with and without SRD; however, patients with SRD show a more significant improvement in macular morphology than those without SRD. Cinal et al.[18] reported that SRD is indicative of significant improvement in BCVA and macular thickness after bevacizumab treatment in SRD-related edema due to central retinal vein occlusion. In our study, the anatomical result at the end of 3 months with bevacizumab loading therapy was improved in the serous group, but it was statistically similar at the 3rd month with the diffuse group. Gallego-Pinazo et al.[10] analyzed the impact of SRD on visual prognosis after repeated intravitreal ranibizumab treatment and found that the presence of SRD may be a key predictive factor for ranibizumab treatment outcomes in patients with BRVO and has no effect on the number of treatments needed among patients with or without SRD at baseline. They also emphasized that patients with SRD show both decreased vision and increased CMT at baseline and that the presence of SRD is associated with a poor visual outcome.[10] In our study, although no statistically significant difference was found, initial vision and macular thickness were high, but the results showed improved vision and macular thickness. Therefore, our study suggests that the presence of SRD in cystoid edema is a good prognostic indicator in anti-VEGF (bevacizumab) therapy.

In BRVO, retinal vein occlusion increases intravascular pressure, particularly in capillaries and post-capillary venules. It also causes the production of chemical intermediates that increase vascular permeability by creating non-perfusion and tissue ischemia. Therefore, both increased intravascular pressure and increased vascular permeability in BRVO play an important role in the development of SRD.[19] The pathogenesis of retinal vein occlusion includes a range of immune and inflammatory changes.[20] Pfister et al.[21] evaluated the levels of inflammatory and angiogenic cytokines in patients with ME secondary to untreated BRVO and correlated the results with OCT parameters. They found that VEGF-A is highly associated with morphological changes, such as SRD. Therefore, anti-VEGF agents are probably highly effective in SRD, in which VEGF plays a role in its pathology. In the study of Choi et al.,[22] cases with and without recurrence after intravitreal anti-VEGF-bevacizumab in macular edema due to BRVO were evaluated in terms of optical coherence tomography angiography (OCTA) findings. There was no difference between the group with and without recurrence in terms of the type of ME before the injection, and no correlation was found between the vascular abnormalities in the OCTA images after ME resolution and the type of initial ME. However, recurrence was found to be associated with areas of non-perfusion in the deep and superficial capillary plexus. Unfortunately, we could not evaluate it with OCTA as a limitation of our study.

Common physiopathological mechanisms have been observed in ME due to vascular diseases of the retina (diabetic retinopathy and so on). The development of ME in diabetes is initiated by fluid accumulation in Müller cells due to the downregulation of Kir4.1 channels, and swelling of Müller cells may cause dysfunction, resulting in Müller cell necrosis.[23] They showed that swelling of the Müller cell cytoplasm may be associated with different types of ME, and the necrosis of Müller cells and death of neuroglia lead to cystoid spaces.[24] In addition, Murakami et al.[24] thought that these ME patterns represent the progression stages of DME and that CME may occur later than the diffuse and serous types. Considering that both diabetes and vein occlusion cause ME with a common physiopathology, it supports the concept that CME alone is actually the last stage of ME and, therefore, may show a poor prognosis, and the treatment response may be reduced.

The limitations of the study are its retrospective design, small number of patients, and short follow-up period. Furthermore, since all patients did not undergo FFA or OCTA after injection, we could not analyze these response differences with the FFA or OCTA results again at the end of the 3rd month.

## Conclusion

In the short term, intravitreal bevacizumab treatment in ME due to BRVO was better in the serous group, both anatomically and visually, compared to that in the cystoid group; however, at the end of the 3rd month, similar results were observed with the diffuse group both anatomically and functionally.

**Ethics Committee Approval:** This study was approved by Kayseri City Hospital Ethics Committee (date: 21.01.2021; number: 278).

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions:** Concept: E.V.; Design: E.V.; Supervision: E.V.; Resource: E.V., E.S.; Materials: E.V.; Data Collection and/or Processing: E.V., E.S.; Analysis and/or Interpretation: L.H.; Literature Search: E.V.; Writing: E.V.; Critical Reviews: E.V., L.H.

**Conflict of Interest:** None declared.

**Financial Disclosure:** The authors declared that this study received no financial support.

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