

## Characteristics of Macular Edema in Behcet Disease after Intravitreal Bevacizumab Injection

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### Abstract

**Purpose:** To investigate the effect of intravitreal bevacizumab (IVB) injection on macular edema (ME) secondary to Behcet's disease.

**Methods:** This prospective case series included 15 patients with bilateral ME due to Behcet's disease. Intravitreal bevacizumab was injected into the more severely involved eye; the contralateral eye was evaluated as the control. Patients were followed up with comprehensive ocular examination, optical coherence tomography, and fluorescein angiography (FA) for a minimum of 6 months by a single ophthalmologist.

**Results:** Patients with a mean age of  $30.6 \pm 7.4$  years received a mean number of 3.3 IVB injections during the 6 months. The mean preinjection vision was  $0.6 \pm 0.3$  and  $0.4 \pm 0.4$  LogMAR in the case and control groups, respectively, with no significant improvement at 6 months. Mean central foveal thickness was  $375.3 \pm 132.1$  and  $307.2 \pm 84.5$   $\mu\text{m}$  in the case and control groups, respectively, and these changed to  $401 \pm 199.9$  ( $P = 0.65$ ) and  $307.7 \pm 82.8$   $\mu\text{m}$  ( $P = 0.73$ ) at month 6, respectively. A statistically nonsignificant improvement in ME was observed during the first 3 months in the case group. However, it did not persist up to month 6 on an as-needed basis. IVB injections caused a disproportionate decrease in the thickness of macular subfields. A reduction in disc leakage was observed on FA ( $P = 0.058$ ). Logistic regression analysis revealed no statistically significant predictive factor for an improvement in visual acuity (VA) and a reduction in foveal thickness.

**Conclusion:** During a 6-month period, IVB injections based on an as-needed protocol provided no statistically significant improvement in VA and ME.

**Keywords:** Behcet's Disease; Macular Edema; Intravitreal Bevacizumab; Uveitis

*J Ophthalmic Vis Res* 2017; 12 (1): 44-52

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Received: 23-12-2015

Accepted: 01-10-2016

### INTRODUCTION

Behcet's disease (BD) is a multisystem vasculitis of unknown etiology.<sup>[1-3]</sup> Ocular involvements are most often

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**How to cite this article:** Ghassemi F, Afshari Mirak S, Chams H, Sabour S, Nilli Ahmadabadi M, Davatchi F, *et al.* Characteristics of macular edema in behcet disease after intravitreal bevacizumab injection. *J Ophthalmic Vis Res* 2017;12:44-52.

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10.4103/jovr.jovr\_254\_15

seen during the early years.<sup>[4,5]</sup> In BD, cystoid macular edema (CME) has been reported to be responsible for visual acuity (VA) less than 20/60, leading to permanent or persistent visual loss in 42% of patients with BD.<sup>[6-8]</sup> Previous studies have reported many systemic treatments with limited success in improving VA (8.8–24.8%) in BD with ocular involvement.<sup>[9-15]</sup>

Vascular endothelial growth factor (VEGF) is a hypoxia-mediated factor that induces the formation of new vessels.<sup>[16]</sup> VEGF is assumed to have a role in the pathophysiology of BD.<sup>[17-20]</sup> Anti-VEGF agents, like intravitreal bevacizumab (IVB), have been shown to be effective in improving VA and reducing CME in eyes affected by uveitis.<sup>[21,22]</sup> A single study in the literature specifically addresses the use of intravitreal anti-VEGF agents for the treatment of CME in patients with BD.<sup>[23]</sup>

Optical coherence tomography (OCT) and fluorescein angiography (FA) are the two most commonly used methods for the evaluation of macular edema (ME) in uveitis. However, OCT is the most appropriate modality for the assessment of ME.<sup>[23]</sup> FA demonstrates the vascular aspects of ME. In some cases, the leakage from the perimacular blood vessels is not associated with increased macular thickness.<sup>[24,25]</sup>

To the best of our knowledge, this study is the largest one describing the ocular morphologic and functional characteristics of ME due to BD before and after IVB injections by using spectral domain OCT (SD-OCT) and FA.

## METHODS

This study was a prospective, nonrandomized, comparative, single-masked, interventional case series in consecutive patients with BD. Institutional review board approval was obtained and the informed consent letter was signed by all participants in the present study. All patients with BD and ME (foveal thickness >300 µm), referred to the Retina Service of Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran, between January 2010 and May 2013, were included. Complete ophthalmic examination, SD-OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany), and 30 × 30° field-of-view FA (HRA-2; Heidelberg Engineering, Dossenheim, Germany) were performed. The specific clinical manifestations referred to the Behcet's disease current activity form and the Iranian Behcet's disease dynamic activity measure score were assessed for each patient at the time of the first examination.<sup>[26,27]</sup>

Retinal thickness values in nine Early Treatment Diabetic Retinopathy Study (ETDRS) subfields were considered. Macular thickness, presence of cystic changes and the size of cysts (classified by diameter: Small, <50 µm; medium, 50–200 µm; and large, >200 µm), presence of the epiretinal membrane (ERM), posterior

vitreal detachment, hyperreflective foci in different layers of the retina called precipitates, and outer retinal integrity including the ellipsoid zone and external limiting membrane were also evaluated.

In FA, early and late vascular leakage, the location (posterior pole, midperiphery, and periphery), extent and severity of leakage (classified by the number of quadrants involved: mild, leakage in one quadrant; moderate, leakage in two quadrants; and severe, leakage in three or more quadrants), any arterial or venous changes (staining, beading, and dilation), and increased foveal avascular zone (>700 µm) were evaluated. Optic disc leakage was classified as mild (on the disc), moderate (leakage less than one disc diameter around the center of the disc), and severe (more than one disc diameter around the center of the disc).

The Snellen chart was used for testing the best corrected VA. After comprehensive ocular examination and acquiring the FA and OCT images, 1.25 µg/0.05 ml bevacizumab (Avastin; Genentech, Inc, South San Francisco, CA, USA) was injected through the pars plana of the eye with more severe ME, and the other eye was considered as the control. After injection, intraocular pressure and retinal artery perfusion were checked, and a topical antibiotic was prescribed for 3 days. Patients were examined the day after and every month thereafter.

Follow-up consisted of comprehensive ophthalmic examination and OCT every month up to 6 months, and FA was performed at months 3 and 6. IVB injection was repeated if the central macular thickness (CMT) exceeded 300 µm on the OCT images of the previously injected eye. Systemic treatment for BD was continued without any modifications. Corticosteroid treatment was the cornerstone of treatment from the beginning. In all cases, 0.5 mg/kg/daily corticosteroid was prescribed, which was gradually adjusted to the patient's need. Immune system suppressants and/or modulators (cyclophosphamide, azathioprine, colchicine, levamisole, and cyclosporine) were also used at the same time as adjuvants, if needed. All patients who needed any change in their systemic treatment during IVB therapy or had other systemic or ocular diseases (diabetes, hypertension, or high refractive error) interfering with the study results were excluded from the study.

Statistical analysis was conducted using SPSS Version 16 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was applied for assessing normal distribution, and parametric and nonparametric tests were used accordingly. Any changes in clinical, OCT, and FA findings were analyzed. Interval data were analyzed at baseline and at months 1, 3, and 6 by using Friedman's test. *dr yazdani* *P* value <0.05 was considered statistically significant, and quantitative values were expressed as mean ± standard deviation. Logistic regression models using robust standard errors were used to assess the ME status and risk factors.

**RESULTS**

Out of 19 patients, 15 with ME due to BD were followed up for 6 months. Four of the 19 patients were excluded because of reactivation of their disease and change of the treatment protocol during the first 3 months. In one of these patients, bilateral avascular necrosis of the femoral head precluded monthly follow-up. Thirteen (86.7%) patients were men and two (13.3%) were women, with a mean age of  $30.6 \pm 7.4$  (range, 20–44) years. The mean duration of uveitis was  $5.11 \pm 2.4$  years, and ME was present for a mean duration of  $1.11 \pm 0.3$  years. All eyes in the case and control groups were panuveitic according to the standardization of uveitis nomenclature with the presence of nonvisually significant posterior subcapsular cataract in five eyes in the case group and four eyes in the control group, without significant changes during the study period. None of the eyes had previously been treated with intravitreal injection of corticosteroids or anti-VEGF drugs. No baseline differences were observed in vision, foveal thickness, and cystic changes between the two groups. Forty-nine IVB injections were

administered in six right eyes and nine left eyes. The number of IVB injections was one in three patients, two in three patients, three in three patients, five in five patients and six in one patient, depending on the response to previous IVB injections. Patients received a mean number of 3.3 injections. In all treated eyes, injections were consequent except for three eyes that needed injections for recurrent ME after 2 months. Three patients had a macular thickness higher than 400  $\mu\text{m}$  at 3 months, and this significantly influenced the mean value. The high macular thickness in these eyes persisted in the following months. Among the clinical findings, only cystic change in the macula was reduced significantly during the 6-month follow-up period [Table 1].

No ocular neovascularization and vitreous hemorrhage were seen in the eyes at the beginning and during the study period. At the beginning, vitritis was present in 20 eyes including trace cells in three, 1+ cells in 12, and 2+ cells in five eyes (13 in the case group and seven in the control group). Three eyes in the case group and two eyes in the control group had vitreous organization at the first visit.

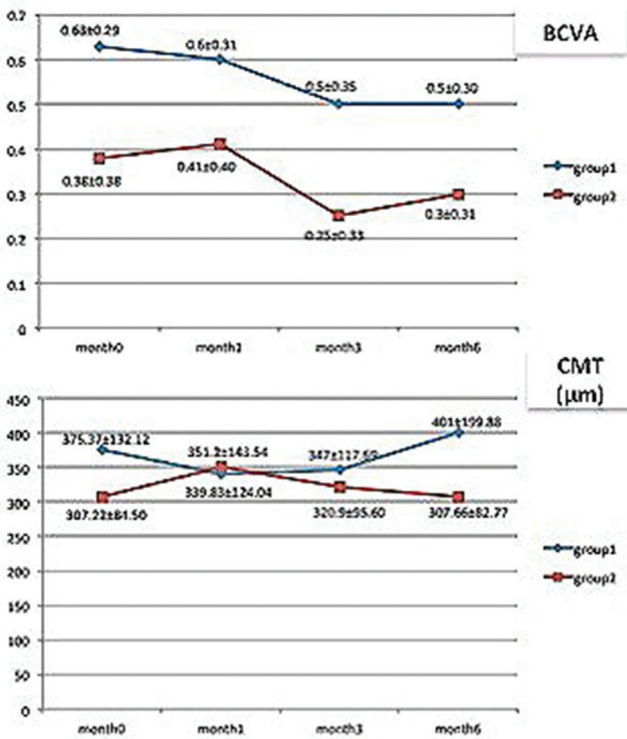
**Table 1. Clinical findings at baseline and during follow-up in the cases and controls**

Clinical variables (Case and Control)	Month 0	Month 1	Month 3	Month 6	Changes in variables during FU time
Visual acuity					
Case	0.63±0.29	0.60±0.31	0.50±0.35	0.50±0.30	0.846 <sup>1</sup>
Control	0.38±0.38	0.41±0.40	0.25±0.33	0.30±0.38	0.930
GEE*	0.462	0.420	0.532	0.743	
Clinical CME	16/30 (53.3%)				
Case	8/15	9/15	5/15	5/15	0.001 <sup>2</sup>
Control	8/15	6/15	4/15	6/15	0.001
GEE *		0.460	0.040	0.401	
		0.317	0.030	0.564	
		0.046*	0.008*	0.014*	
		0.317	0.317	0.564	
Vitritis	20/30 (66.6%)				
Case	13/15	9/15	9/15	10/15	0.544 <sup>2</sup>
Control	7/15	6/15	4/15	6/15	0.040
GEE*	0.050	0.260	0.889	0.928	
Vascular sheeting	1/30 (3.3%)				
Case	1/15	2/15	1/15	1/15	0.677 <sup>2</sup>
Control	0/15	0/15	0/15	0/15	1.000
GEE*	0.050	0.260	0.889	0.928	
Hard exudates	1/30 (3.3%)				
Case	1/15	2/15	0/15	1/15	0.423 <sup>3</sup>
Control	0/15	0/15	0/15	0/15	1.000
GEE*	-	0.477	-	-	
CWS	2/30 (6.7%)				
Case	2/15	0/15	0/15	0/15	0.677 <sup>2</sup>
Control	0/15	0/15	0/15	0/15	1.000
GEE*	0.470	-	-	-	

CME, cystoid macular edema; CWS, cotton wool spot; FU: follow-up; \*Generalized Estimating Equation adjusted for age, sex, and number of injections; <sup>1</sup>Based on Friedman test; <sup>2</sup>Based on Kendall’s coefficient of concordance

The mean VA was  $0.6 \pm 0.3$  LogMAR in the case group and  $0.4 \pm 0.4$  LogMAR in the control group at baseline. The improvement in VA during the 6 months (monthly and from month 0 to months 3 and 6) was not significant in either group [Figure 1]. The changes in CMT were not significant during the 6-month period in either group (Friedman and Wilcoxon tests) [Figure 1]. By omitting three outliers and reanalyzing the data, although some fine trends in improvement of vision were observed, it was not statistically significant probably because of the small sample size [Figure 2].

Table 2 shows the baseline OCT characteristics and their changes during the follow-up period. Some statistically nonsignificant changes were observed in the retinal precipitates at month 3. By month 6, the changes were not as significant as those at the first visit. At the beginning, cystic changes included small-sized cysts in nine eyes, medium-sized cysts in seven eyes, and large-sized cysts in seven eyes (some eyes had different-sized cysts). The size of cysts changed after the IVB injections. At the first visit, 63.6% of the cysts were small, and this changed to 77.3%, 75%, and 81.8% at months 1, 3, and 6, respectively. In three eyes, only the inner nuclear layer (INL) was involved, whereas the cysts were in the INL, outer nuclear layer, and outer plexiform layer in eight eyes [Figure 3].



**Figure 1.** Changes in visual acuity (best corrected visual acuity [BCVA]; LogMAR) and central macular thickness (CMT; µm) after intravitreal bevacizumab injection in cases (group 1) and controls (group 2) during the 6-month follow-up period.

Macular thickness in multiple ETDRS subfields was evaluated on OCT images. Statistical analysis showed more thickness changes in the superior subfields of the fovea in the IVB treated group from month 0 to 6 ( $P = 0.035$  for the superior perifoveal area and  $P = 0.012$  for the superior parafoveal area). The reduction in the inferior perifoveal area in the same group was also significant from month 0 to 1 ( $P = 0.047$ ). The thickness of the other areas did not show any significant changes during the 6-month follow-up period.

Table 3 presents the FA findings at baseline and during the 6-month follow-up period. Improvement in optic nerve head leakage, unrelated to neovascularization, was detected at month 3. Other angiographic parameters were not influenced by the IVB injections.

The association between OCT changes (cystic changes, subretinal fluid [SRF], and macular thickness) and leakages on FA and VA at baseline were evaluated. The presence of cystic changes was associated with poorer VA ( $P = 0.005$ ) and increased subfield thicknesses (foveal thickness:  $P < 0.001$ ; nasal parafoveal thickness:  $P = 0.001$ ; nasal perifoveal thickness:  $P = 0.009$ ; temporal parafoveal thickness:  $P = 0.008$ ; superior parafoveal thickness:  $P < 0.001$ ; superior perifoveal thickness:  $P = 0.008$ ; and inferior parafoveal thickness:  $P = 0.009$ ) were also associated with poor vision. Irrespective of the location of leakage, a relationship between the presence of cysts and vascular leakage ( $P = 0.026$ ) was detected. Furthermore, a direct association was observed between the presence of cysts and extent of leakage ( $P = 0.022$ ). No correlation was found between the presence of SRF and VA ( $P = 0.955$ ,  $r = -0.013$ ) at the first visit. No correlation was found between leakage severity and VA ( $P = 0.726$ ,  $r = 0.079$ ) either. Moreover, no correlation was found between the occurrence of the ERM and aggravation of vision ( $P = 0.070$ ,  $r = 0.394$ ) and foveal thickness ( $P = 0.334$ ,  $r = 0.216$ ).

## DISCUSSION

In this comparative case series, the morphologic and functional characteristics of persistent ME in patients with BD were evaluated before and after IVB injection. The severity of vascular leakage correlated with cystic changes in the macula. Expectedly, the presence of cystic changes was associated with a lower VA. During 6 months, IVB injections resulted in a statistically nonsignificant improvement in VA and ME, and a significant decrease in disc leakage on FA images.

The pathogenesis of uveitic ME is poorly understood, and a mechanism involving multiple mediators may be involved.<sup>[28,29]</sup> This multisystem disease has been described to have a multigenic susceptibility background, and the induced inflammation involves multiple mediators.<sup>[30]</sup> Multimodal treatment seems to have more efficacy with fewer side effects.<sup>[31]</sup>

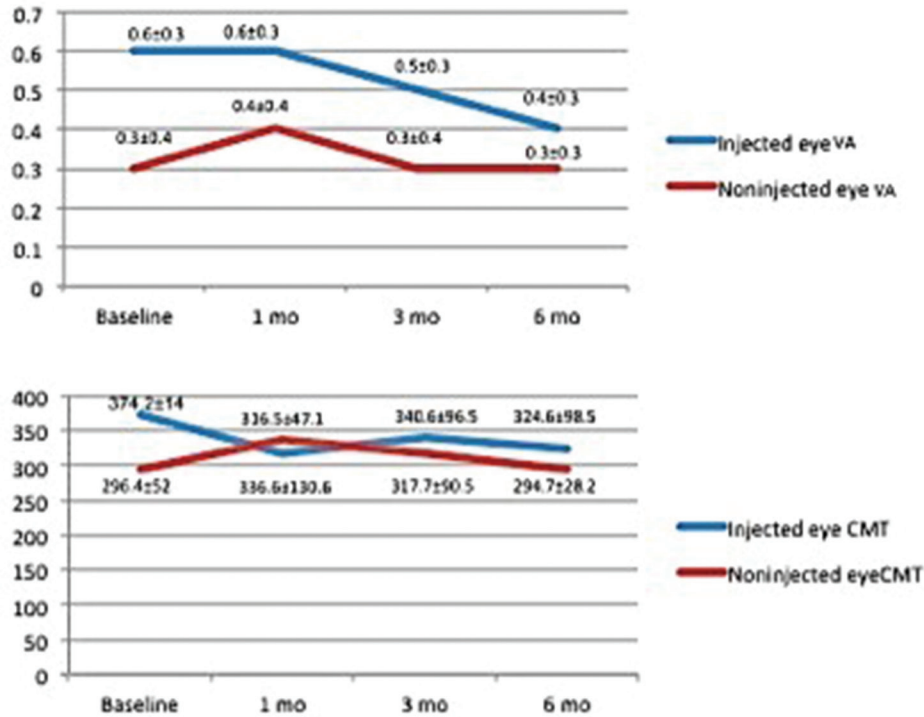
**Table 2. Baseline and follow-up optical coherence tomography (OCT) characteristics in both cases and controls**

OCT Variables (Case and Control)	Month 0	Month 1	Month 3	Month 6	Changes in variables during FU time
CMT					
Case	375.37±132.12	351.20±143.54	347.87±117.69	401.00±199.88	0.906 <sup>1</sup>
Control	307.22±85.50	339.83±124.04	320.90±95.60	307.66±82.77	0.558
GEE*	0.085	0.072	0.074	0.625	
Five Central macular sub-segments thickness					
Case	1994.37±359.74	1928.91±340.17	1871.91±347.71	2070.83±584.64	0.858 <sup>1</sup>
Control	1767.05±265.73	1863.70±369.25	1785.18±276.22	1777.67±226.90	0.983
Group 2			0.612		
GEE*	0.194	0.183	0.109	0.668	
Cystic change	11/30 (36.6%)				
Case	8/15	4/15	5/15	4/15	0.392 <sup>2</sup>
Control	3/15	1/15	3/15	3/15	0.261
GEE*	0.189	0.109	0.619	0.741	
Precipitates <sup>‡</sup>	25/30 (83.3%)				
Case	13/15	10/15	11/15	12/15	0.392 <sup>2</sup>
Control	12/15	11/15	11/15	12/15	0.392
GEE*	-	0.477	-	-	
ERM	13/30 (43.3%)				
Case	8/15	8/15	9/15	10/15	0.112 <sup>2</sup>
Control	5/15	6/15	8/15	10/15	0.013
GEE*	0.669	0.903	0.142	0.866	
PVD	7/30 (43.3%)				
Case	2/15	2/15	3/15	3/15	0.392 <sup>2</sup>
Control	5/15	5/15	2/15	4/15	0.572
GEE*	0.247	0.080	0.247	0.413	
Impaired outer retina	18/30 (60%)				
Case	6/15	6/15	8/15	8/15	0.392 <sup>2</sup>
Control	12/15	10/15	9/15	11/15	0.794
GEE*	0.461	0.779	0.416	0.171	
Subretinal fluid	1/30 (3.33%)				
Case	1/15	0/15	0/15	1/15	0.261 <sup>2</sup>
Control	0/15	1/15	1/15	0/15	0.261
GEE*	0.715	0.715	0.715	0.715	
Ellipsoid zone abnormality	4/30 (13.3%)				
Case	3/15	3/15	1/15	2/15	1.000 <sup>2</sup>
Control	1/15	1/15	1/15	1/15	1.000
GEE*	0.461	0.779	0.416	0.171	
Fusion of layers	3/30 (10%)				
Case	2/15	2/15	1/15	2/15	0.906 <sup>2</sup>
Control	1/15	1/15	1/15	0/15	0.733
GEE*	0.789	0.715	0.368	0.322	

CMT, central macular thickness; ERM, epiretinal membrane; PVD, posterior vitreous detachment; FU, follow-up; <sup>‡</sup>Precipitates were mostly seen in ganglion cell layer. \*Generalized Estimating Equation adjusted for age, sex and number of injections, <sup>1</sup>Based on Friedman test, <sup>2</sup>Based on Kendall's Coefficient of Concordance

Intravitreal injection allows rapid delivery of high concentrations of the drug into the eye as it bypasses the blood-ocular barriers and is simultaneously associated with the lowest incidence of drug related

systemic toxicity.<sup>[32]</sup> In our study, the most common posterior segment findings were vitritis and ME. Clinical resolution of ME was observed during the 6-month follow-up period. A reduction of macular thickness was



**Figure 2.** Changes in best corrected visual acuity (BCVA; LogMAR) and central macular thickness (CMT; μm) after intravitreal bevacizumab injection in cases (group 1) and controls (group 2) after removing the outliers (three refractory cases) during the 6-month follow-up period.

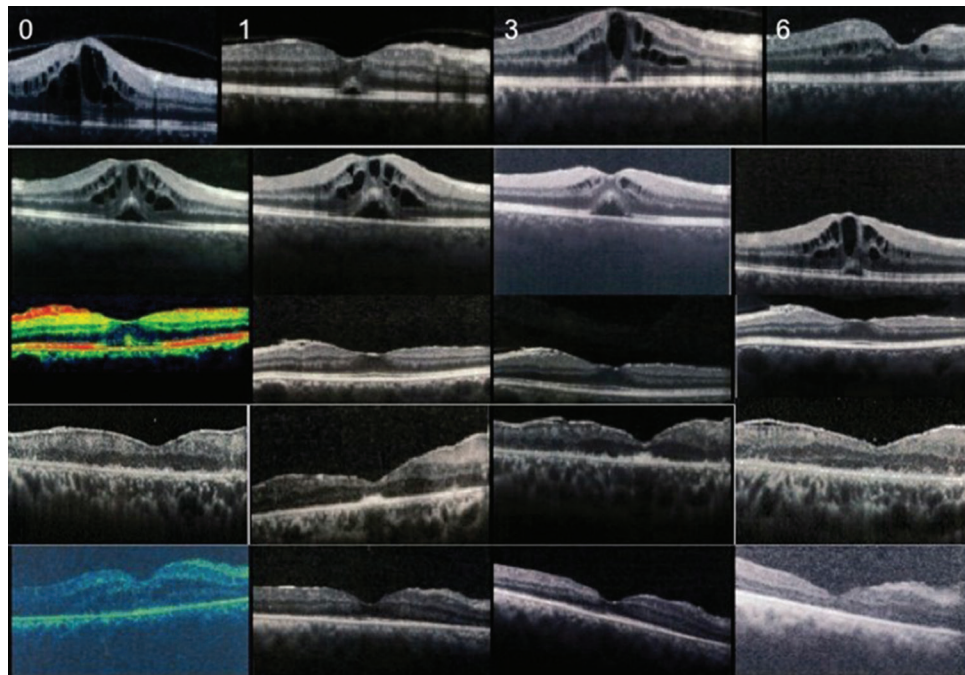
**Table 3. Fluorescein angiographic findings at baseline and during follow-up in both treatment and control groups**

FA variables (Case and Control)	Month 0	Month 3	Month 6	Changes in variables during FU time
Early leakage <sup>†</sup>	19/30 (63.3%)			
Case	9/15	9/15	9/15	1.000
Control	10/15	12/15	11/15	0.157
GEE *	0.400	0.293	0.173	
Late leakage <sup>†</sup>	27/30 (90%)			
Case	10/15	13/15	14/15	0.368
Control	13/15	15/15	10/15	0.157
GEE *	0.449	0.335	0.003*	
Disc leakage	19/30 <sup>§</sup> (63.3%)			
Case	11/15	5/15	5/15	0.135
Control	13/15	10/15	9/15	0.417
GEE*	0.415	0.027	0.053	

\*Generalized estimating equation adjusted for age, sex, and number of injections; <sup>†</sup>Peripheral area was the most common area of leakage; FA, fluorescein angiography; FU, follow-up; Friedman test<sup>‡</sup>; Kendall’s coefficient of concordance<sup>2</sup>

also observed in different subfields of OCT during the 6-month period. As the presence of edema may have a negative impact on VA, the reduction in edema could explain the trend for visual improvement in this case series. A disproportionate decrease in the thickness of different subfields was seen after IVB injections, possibly because of the convective movement of the vitreous fluid leading to more concentration of bevacizumab in the superior subfields.

Figure 1 shows a reduction in CMT during the first month and its stability up to month 3, followed by a steady and slow rise after 3 months. As patients received a mean number of 3.3 injections, mostly as consequent injections during the first few months, and CMT increased after month 3, it is likely that regular and more repeated IVB injections could have resulted in a better outcome. However, it should be stated that the very high thicknesses in three patients influenced



**Figure 3.** Optical coherence tomography (OCT) changes in the intravitreal bevacizumab (IVB)-injected eyes in five patients with Behcet's disease. The OCT changes in thickness after IVB injection at months 0, 1, 3, and 6 are shown consecutively.

the mean thickness value during this time period. The statistical nonsignificance of the findings could be related to the small sample size of this study.

Twenty percent of the patients in this series received just a single IVB injection, 6.7% of them received six injections, and 40% received five or six injections during 6 months for controlling the ME. Previous studies<sup>[33-35]</sup> have reported a transient effect from IVB on improvement of CME in inflammatory eye diseases and the need for repeating injections. Bae et al reported more efficacy of IVB in uveitic CME in the first 4 weeks, which worsened thereafter until week 12.<sup>[35]</sup> They reported IVB as a well-tolerated and effective supplementary therapy for persistent CME in Behcet's uveitis.<sup>[33-35]</sup> Mirshahi et al, in their noncomparative case series on 12 eyes of 11 patients with CME due to BD, showed an improved VA in seven eyes at month 1 after a single injection of bevacizumab.<sup>[23]</sup> CMT and angiographic characteristics remained unchanged in their study.<sup>[23]</sup>

There is no consensus regarding the correlation between macular thickness and VA.<sup>[36-38]</sup> Cordero et al reported an improvement in VA of 2 or more lines in 38.4% of patients after a single intravitreal injection of 2.5 mg bevacizumab for uveitis resistant CME.<sup>[22]</sup> Another study reported a similar result: improvement in VA by more than 2 lines within 4 weeks in 40% of patients with refractory CME.<sup>[35]</sup> In our study, the improvement in VA after IVB injections over 6 months was higher in the case group than in the control group, but the difference was not statistically significant [Figure 1]. The statistical nonsignificance of these findings could be related to the small sample size of this study.

Our results showed an association between the presence of cysts (independent of cyst size and location) with poor VA and higher macular thickness. IVB was effective in reducing the size of cysts and optic nerve head leakage, indicating the anti-inflammatory effect of IVB [Table 3].

VEGF is considered the main factor responsible for neovascularization and increased vascular permeability in BD.<sup>[16,39-41]</sup> In addition, the concentration of VEGF in the aqueous humor of eyes with uveitic CME is higher than that in eyes with uveitis without CME.<sup>[37]</sup> Many reports have shown the positive effects of anti-VEGF agents in reducing vascular leakage in other VEGF-related diseases such as AMD (age related macular degeneration) and DME (diabetic macular edema).<sup>[42,43]</sup> Intraocular VEGF titration would be needed for better understanding this theory in patients with uveitis and for determining the exact dosage needed for BD induced ME.

The limitations of our study are the small sample size, limited follow-up time, and as-needed dosing of IVB that precluded any judgments about the long-term efficacy of IVB in BD. Monthly injections and higher doses could be investigated in future studies with larger sample sizes.

In conclusion, IVB provided a nonsignificant increase in VA and an improvement in macular thickness that was not consistent during the 6-month follow-up period. A significant reduction in angiographic disc leakage was observed. Larger studies with longer follow-up durations examining different doses, types, and frequencies of anti-VEGF drugs are suggested.

## Financial Support and Sponsorship

Research deputy of TUMS.

## Conflicts of Interest

There are no conflicts of interest.

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