

OCTA Biomarkers in Sight-Threatening Behcet's Disease-Related Uveitis Treated with Adalimumab

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Abstract

Background: The use of adalimumab in the treatment of Behcet's disease-related uveitis has been demonstrated to be safe and effective in a recent large retrospective study. This study aimed to evaluate the effectiveness of OCTA in detecting abnormalities in the retinal microvasculature following remission achieved with adalimumab treatment.

Aim of Study: To evaluate retinal microvasculature parameters during Behcet's uveitis (BU) remission status reached post treatment with adalimumab via optical coherence tomography angiography (OCTA), and compares the results with those from healthy eyes.

Material and Methods: A total of 10 eyes of 10 BU patients presenting during the remission period (within 12 months) of BU involving the posterior segment were enrolled, as were 20 normal eyes of 20 age and sex-matched healthy participants. OCTA images were analyzed. Foveal avascular zone (FAZ), and vessel densities (VD) were calculated and compared.

Results: 10 eyes of 10 BU patients and 20 normal eyes of 20 age and sex-matched subjects were included in the study. At baseline, the all 10 eyes had active retinal vasculitis. Retinal vasculitis resolved in all cases (100%) after starting adalimumab. The mean time to complete resolution of inflammation was 3.4 weeks. None of the patients developed any adverse events associated with adalimumab treatment. The FAZ was higher in the BD group than in the control group ($p=0.01$). Both the superficial and deep plexuses vessel densities were significantly lower in BD eyes ($p<0.05$).

Conclusion: BD can cause irreversible damage to the retinal circulation affecting both SCP and DCP. OCTA gives a full view of the retinal microvasculature. Adalimumab was effective in preventing irreversible sight-threatening BD. Adalimumab treatment appears to be associated with improvement of the retinal blood flow more evident in the DCP thus provide better final visual outcome for cases with BD uveitis.

Key Words: Behcet's disease – Adalimumab – Intraocular inflammation – Retinal vasculitis – Uveitis.

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Introduction

BEHCET'S disease (BD) is a multisystem inflammatory disorder that affects skin, joints and eyes. The ocular features include posterior uveitis, retinal vasculitis, glaucoma, cataract formation and secondary ocular infections [1].

The incidence of uveitis in BD varies from 21% to 60% depending on ethnicity and diagnostic criteria used [2]. The changes in the macular area as a consequence of recurrent vasculitis attacks may result in decreased visual acuity, color vision defects, loss of contrast sensitivity, or metamorphopsia [3,7,8].

Sight threatening behcet uveitis is a debilitating and often-blinding inflammatory condition of the eye. Although BD-specific immunomodulatory therapies have been developed in the past, they have significant side effects and can often lead to serious adverse events. Thus, there is a need for new and safer therapies that target the inflammatory response in patients with uveitis associated with BD. One such treatment is an anti-TNF thereby such as adalimumab, which blocks the production of TNF- α , a key cytokine involved in immune cell activation and inflammation also plays an important role in the inflammatory process associated with Behcet's disease [4,5].

Optical coherence tomography angiography (OCTA) is a novel non-invasive imaging modality that allows the clinician to observe retinal vessels without the assistance of a contrast agent. This technique provides high-resolution images of the superficial and deep capillary plexuses within the retina and is commonly used to identify the presence of various ocular diseases such as diabetic retinopathy, vascular occlusion, posterior uveitis,

vasculitis and age-related macular degeneration [6,9,10,11].

The objective of this study is to provide new insight into the clinical benefit of anti-TNF- α (adalimumab) agents in the treatment of sight-threatening uveitis in patients with Behcet's disease and to evaluate the effectiveness of OCTA in detecting abnormalities in the retinal circulation following treatment with adalimumab and to compare these results with normal age matched control.

Material and Methods

This cross sectional study included 10 eyes of seven patients who were diagnosed with unilateral severe sight threatening posterior uveitis. All the 10 patients were treated with subcutaneous adalimumab. All patients were diagnosed and followed-up in Kafr El-Sheikh and Tanta University Rheumatology and Ophthalmology Departments in the period between August 2021 and August 2022.

The risks and benefits of adalimumab and alternative therapies were fully explained, and consent for treatment was obtained from the patients. Informed consent was obtained from patients for publication.

The patients were diagnosed as BD based on the International Study Group criteria for BD. Severity of ocular involvement and response to treatment were evaluated according to the Standardization of Uveitis Nomenclature (SUN) Workgroup criteria [12]. Sight threatening posterior uveitis was defined by the presence of vitreous cells in addition to at least one of the following: (1) vasculitis: Vascular sheathing clinically and leakage on FFA, (2) retinitis: Retinal infiltrates, and/or (3) papillitis / papillopathy: Optic disc swelling clinically or hyper fluorescence on fundus fluorescein angiography (FFA) [13].

All patients included in the study were started on adalimumab when they developed sight-threatening relapse episodes that varied from dense vitritis, focal or multi-focal retinitis or evidence of retinal vasculitis.

Complete response was referred as the remission phase with no detection of keratic precipitates, hypopyon, retinitis, vitritis, vasculitis, papillitis, or macular edema for more than 3 months.

Exclusion criteria were dense media obstacles, trauma, other retinal diseases causing uveitis and retinal vascular occlusive disease unrelated to BD, diabetic retinopathy, hypertension and optic nerve diseases such as glaucoma or optic neuropathy.

A complete ophthalmologic examination was performed for all patients including measurement of Snellen best-corrected visual acuity; slit-lamp examination, IOP measurement, and dilated fundus examination were recorded.

Seven eyes from 10 patients presenting to an ophthalmology department after the resolution of the posterior segment following adalimumab therapy were imaged by OCTA using the commercial spectral domain OCT system (Avanti RTVue-XR; Optovue, Fremont, CA), which is based on the AngioVue Imaging System to obtain amplitude decorrelation angiography images. It is a dual modality OCT-based system, capable of imaging both function and structure of ocular microvasculature.

A-scan rate of this machine is 70,000 scans per second, using a light source centered on 840nm and a bandwidth of 50nm. The tissue resolution is 5 μ m axially, and the beam width is 20 μ m. Each OCTA volume have 304 x 304 A-scans with two consecutive B-scans captured at each fixed position before proceeding to the next sampling location. Split-spectrum amplitude-decorrelation angiography (SSADA) was used to extract the OCT angiography information. Each OCTA volume is acquired in 3s, and two orthogonal OCTA volumes were acquired in order to perform motion correction to minimize motion artifacts arising from microsaccades and fixation changes. Angiography information displayed is the average of the decorrelation values when viewed perpendicularly through the thickness being evaluated. The images were captured with a scan area 3 x 3mm.

OCTA images of the SCP and DCP were acquired using the automated software algorithm. Based on these default settings, the boundaries of SCP extended from 3 μ m below the internal limiting membrane to 15 μ m below the inner plexiform layer.

A 30 μ m thick layer from the inner plexiform layer was used to visualize the DCP. If the segmentation scans were not perfectly aligned according to the parameters defined above, editing and propagation tool automatically applies the manually corrected segmentation to the OCT B scans and propagates the correction to the adjacent B scans as well, in order to obtain a well delineated detailed image of enface slab for qualitative and quantitative analysis. The calculations were performed over the foveal region.

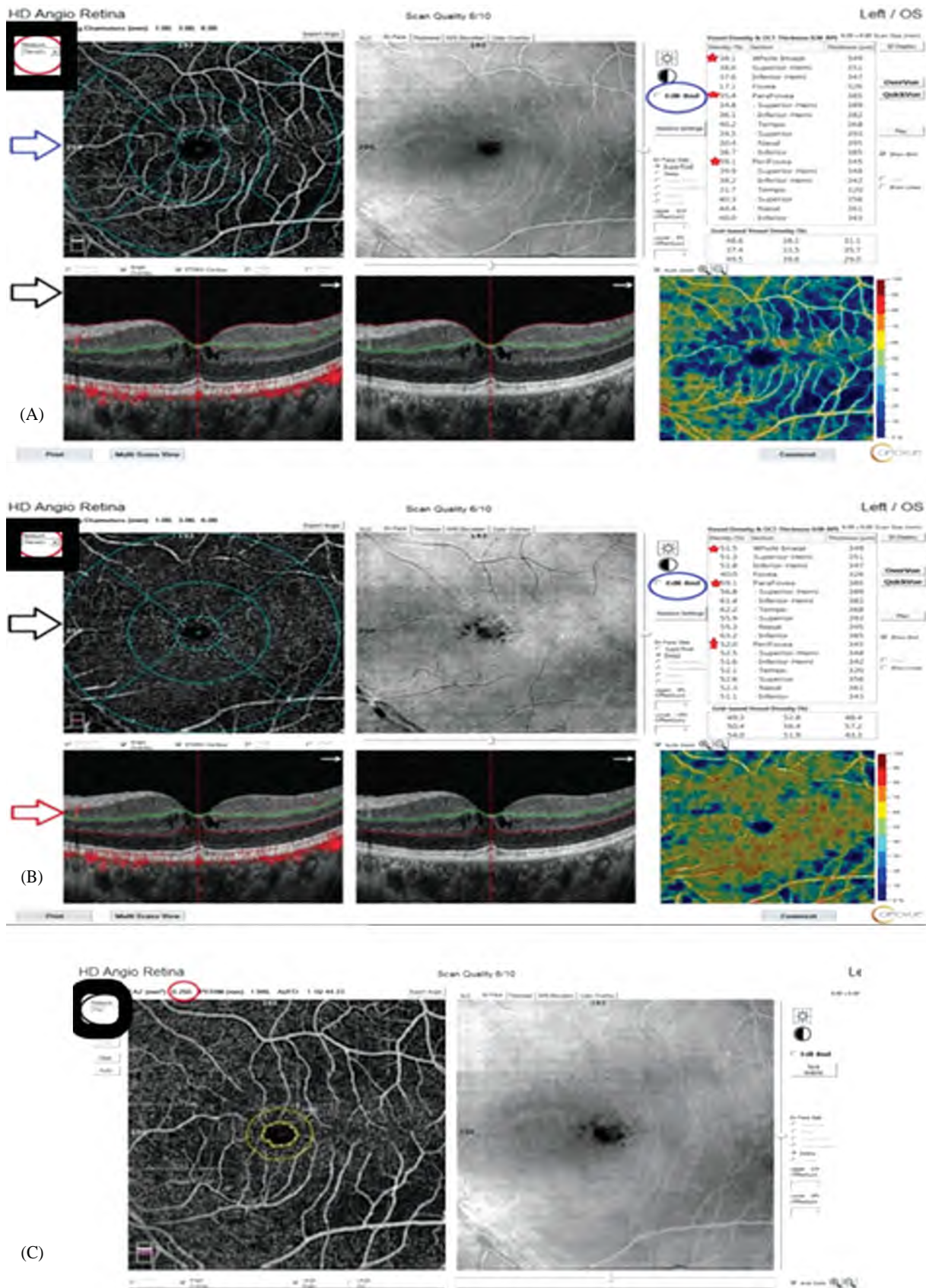


Fig. (1): OCTA and SD-OCT parameters measured: (A): SCP density display: The density parameter is chosen (red circle), the VD as a % of the area is displayed in the top right table, the whole image was recorded for use in this study (red stars). (B): DCP density display: The density parameter is chosen (red circle), the VD as a % of the area is displayed in the top right table, the whole image was recorded for use in this study (red stars). (C): FAZ area display (black circle), automatic detection and delineation of the FAZ area (white dotted yellow circle), documentation of the FAZ area in mm² for the purpose of this study (red circle).

Angio Analytics software is quantification tools that enable measurement of vessel density and non flow area to measure the size of the FAZ. Vessel density map was used to evaluate the relative density of flow of the global image at the level of the SCP and DCP, as a percentage of the entire area. Using the acquired images, the FAZ area was measured in square millimeters (mm²), using the non flow tool on the OCTA software. When the center of the FAZ is marked, the area of FAZ is automatically calculated by the software (RTVue-XR version: 2017.1.0.151).

Ethics considerations:

The study protocol was approved by the local ethics committee. All patients provided informed consent to participation in the study, and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

Statistical method:

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 24. Descriptive statistics were reported by mean and standard deviation. Analyses were done for parametric quantitative data between the two groups using independent samples *t*-test, and for nonparametric quantitative data using Mann-Whitney test between the two groups. The level of significance was taken at (*p*-value <0.05).

Results

A total of 10 eyes of 10 BD patients and 20 normal eyes of 20 healthy participants were included in the study based on the quality of OCTA images. Their Demographic data were tabulated (Table 1).

Table (1): Comparison of demographic characteristics of the studied groups.

	Independent Samples Test									
	Levene's Test for Equality of Variances		<i>t</i> -test for Equality of Means							
	F	Sig.	<i>t</i>	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference		
								Lower	Upper	
<i>Sex:</i>										
Equal variances assumed	155.556	.000	-2.079	25	.048	-.4000000	.1924281	-.7963131	-.0036869	
Equal variances not assumed			-3.559	19.000	.002	-.4000000	.1123903	-.6352356	-.1647644	
<i>Age:</i>										
Equal variances assumed	.134	.718	1.460	25	.157	.47143	.32288	-.19356	1.13642	
Equal variances not assumed			1.395	9.748	.194	.47143	.33797	-.28427	1.22712	

Mean best-corrected visual acuities according to the Snellen system were 1.0 in control eyes and 0.4 (range 0.3-1.0) in BD eyes. Table (1) shows the demographical features of the participants. There was no significant difference in age, sex, or spherical equivalents between the control group and the BD group (Table 1); BCVA was significantly worse (*p*<0.001) and signal-strength index was lower (*p*=0.007) in the BD group. The FAZ and all VDs in both layers were in accord with normal distribution (*p*>0.05).

The 10 eyes presented with panuveitis, among them 5 eyes presented with active retinal vasculitis. Also, three patients were single eyed with the presenting eye was pseudophakic with panuveitis and the fellow eyes had foveal scars with advanced visual field loss. After starting adalimumab treatment the seven eyes had complete improvement

of inflammation, with decrease of cellular reaction as to <0.5 in anterior chamber and vitreous. Also there were no signs of vasculitis on fundus examination. Complete resolution of inflammation was noted after a mean of 3.4 weeks (median = 4 weeks; range = 2-4 weeks).

The mean vessel density of the superficial capillary plexus in the Behcet's group was 33.19 ±3.35% that was significantly lower than the normal group, which was 50.31±1.88%; *p*<0.001. The mean vessel density of the deep capillary plexus in the Behcet's group was 45.23±8.9% that was significantly lower than the normal group, which was 54.76±3.13%; *p*<0.001. The mean area of the FAZ in the Behcet's group was 0.68±0.15% that was significantly higher than the normal group, which was 0.30±0.08%; *p*<0.001. Moreover, the mean vessel density of the superficial capillary

plexus in the Behcet's group was significantly lower than the deep capillary plexus; $p < 0.001$ (Table 2).

Table (2): Comparison of vessel density in SCP and DCP between post treatment with Adalimumab Behcet Group and Control group.

	Test statistics		
	VD SCP	VD DCP	FAZ
Mann-Whitney U	.000	16.000	.000
Wilcoxon W	28.000	44.000	210.000
Z	-3.873	-2.988	-3.875
Asymp. Sig. (2-tailed)	.000	.003	.000
Exact Sig. [2*(1-tailed Sig.)]	.000 ^b	.002 ^b	.000 ^b

b: Not corrected for ties.

Discussion

Due to the considerable adverse effects of corticosteroids, clinicians confront enormous difficulties when starting treatment with them in uveitic patients. Biologics, particularly anti-TNF alpha medications, are among of the effective alternatives for treating uveitis that could result in blindness [14].

The EULAR consensus suggests that in cases of severe, sight-threatening BD related uveitis, anti-TNF alpha could be used as first-line therapy. This also was proven by recent research [15,16].

Numerous prospective and retrospective trials in the adult population showed that 6-33% of uveitis causes are BD-related. Adalimumab's stated effectiveness for reducing inflammation in these studies ranged from 38 to 90% [17].

To determine this efficacy studies used a variety of outcome criteria, including as total disease quiescence, a two-step reduction in anterior chamber inflammation, and a total corticosteroid sparing effect. One of these studies, by Diaz-Llopis et al., [18], revealed the potential for a higher prevalence of aggressive uveitis in younger patients. They reported a satisfactory outcome with adalimumab treatment in uveitis in a relatively large sample size of 131 cases (9.9% BD uveitis) in a relatively young age group (mean age of 27 years old). According to Biester et al., the majority of patients (86%) with refractory uveitis were able to reduce their anterior chamber reactivity by two grades when taking adalimumab [19].

Based on a pediatric cohort with 16.7% BD-related uveitis, Ho et al., recently revealed that 84.2% of cases might achieve complete steroid sparing effect with anti-TNF alpha therapy [20].

However, BD-related posterior uveitis frequently manifests in younger patients as a more aggressive uveitis [21]. Our also results showed that adalimumab is capable of achieving remission with complete resolution of posterior uveitis in 100% of cases.

According to our knowledge, this study is the first to use OCTA to assess the retinal microvasculature in BD patients during the remission phase of BD reached with adalimumab therapy, we carried out quantitative measurement of retinal microvasculature and FAZ area in the superficial and deep capillary plexuses and contrasted the outcomes with those obtained from healthy eyes. Even throughout the time of remission, the FAZ in BU eyes enlarged, and the superficial and deep capillary plexuses both had decreased VD. It's well known that the gold standard imaging method for determining the FAZ area and learning more about the non perfusion area in the diagnosis of BD is FFA. However FFA has notable limits. The investigator have to measure FAZ during the early angiography phases as fluorescein leaking during late phases from abnormal vessels can result in an overestimate of the non perfusion and underestimation of FAZ area [22].

One significant benefit of OCTA is that it makes it easier to assess bilaterally the FAZ area and non perfusion regions without interference from dye leakage [23]. Another is that it can be used to assess the choriocapillaris, outer retinal circulation, and inner retinal circulation (SCP and DCP) individually. Additionally, the retinal vasculature blood flow and vessel density can be quantitatively analyzed using newly developed software.

In earlier studies, FAZ area in BD eyes and control eyes did not differ statistically using OCTA during the active period of BD [8]. However, in the current study, we conducted on patients with BD who were in their remission period; the FAZ area in BD eyes was considerably larger than those in control eyes. Patients with various retinal ischemia disorders, such as diabetic retinopathy and retinal vein occlusion, have been found to have enlarged FAZs [10,24,25,26].

The main OCTA finding in the current study was the decreased VD in the inner retinal circulation after Behcet's uveitis remission. This could be explained by a number of different mechanisms and histopathologic finding in eyes with BD. Most importantly is that retinal vasculature is obliterated and occurrence of necrotizing vasculitis [27].

In eyes with active BD, Khairallah et al., found microvascular alterations and noted that the vascular density values were lower than in healthy eyes [10].

It was proposed that localized defects in the retinal nerve fiber layer (RNFL) are the cause of focal retinal atrophy. These defects may also be the cause of non perfused or hypoperfused regions involving both the superficial and deep retinal plexuses along the pathway of the affected retinal fibers [28].

Aksoy et al., conducted a study on Thirty-five eyes of 35 BD patients and 30 normal eyes of 30 age and sex-matched subjects and found that the FAZ was substantially higher ($p < 0.001$) than control group. Also they found that DCP vessel densities were significantly lower in BD eyes ($p < 0.05$) [29].

OCTA was carried out on patients by Cheng et al., [30] while their BD was in remission. They found considerable DCP alterations and proposed that disruption of the outer retina, including disarray of the ellipsoid zone and interdigitation zone bands, is caused by ischemia, particularly in the DCP. They also proposed that alterations in the inner retinal vasculature may be related to the outer retinal disruption and choroidal abnormalities seen in BD patients. But they also founded that, in the SCP capillary involvement tended to be more severe than that of the small vessel. Furthermore the retinal capillaries are more frequently affected than the retinal veins in patients with posterior Behcet's uveitis, according to FA research done by Atmaca et al., [31,32].

It is believed that increased production of sticky proteins on the vascular endothelium, which encourages capillary occlusion, as well as inflammatory cells penetrating vessel walls and narrowing the lumen, are what contribute to the decreased vascular density during activity [33].

However our results showed decrease in the vessel density in the SCP and DCP when compared to control. Also we found that on comparing the SCP and DCP VD after controlling the sight threatening uveitis attack with adalimumab, the DCP showed improved VD values than SCP in contrary with the previously mentioned studies. We assume this may be favorable effect of adalimumab as improving the deep retinal plexus circulation is crucial for outer retinal layers most importantly the ellipsoid zone integrity and subsequently the final visual prognosis in such sight threatening Behcet uveitis attacks. This was also noted and proved by Wassef et al., [34] who conducted a A

prospective longitudinal observational analytic study on patients with active BD and also assessed by OCTA and enhanced depth imaging OCT during activity and after remission, for retinal microvascular and subfoveal choroidal thickness changes. Their Results showed that with remission of active posterior uveitis, capillary density in both layers increased, while the FAZ area increased. But Accourinti et al., [35] stated that no statistically insignificant improvement in DCP and backed their results by the theory proposed by Somkijrungraj et al., [23] that deep capillary affection in BD occurs at an early stage of the disease and proceeds regardless of the activity status of the disease but rather correlates positively with the number of reported attacks, and thus there tends to be a bigger irreversible component of the hypoperfusion in the deep plexus than the superficial.

Adalimumab was shown to improve ocular inflammation as measured by clinical examination also OCTA showed improvement of the VD of the DCP.

Our findings imply that OCTA imaging of the inner retinal vasculature may be a practical and accurate method of determining the involvement of the vasculature during BD remission. Also clinicians should be able to monitor patients during follow-up visits and gauge the effectiveness of treatment with the aid of a sensitive retinal plexus evaluation via OCTA.

It should be emphasized that there are a number of restrictions on the current study. First of all, because of the small sample size, we are unable to make any firm judgments regarding the quantitative characteristics of the inner retinal vasculature and their relationship to pathological changes in the outer retina. Secondly it should be noted that the signal-strength signal was less in BD eyes than in control eyes, which may be related to media opacity. It was anticipated and could affect VD measurements. Third, only 3 x 3-mm images were used to quantify vascular characteristics. Given the trade-off between scan size and image clarity in the OCTA system, a small scanned region nevertheless ensures accurate measurement of the FAZ and VD. Furthermore, even though only a small portion of the macular area was scanned, we still found a big difference between the BD group and the control group.

Our findings indicate that algorithm-based OCTA has the potential to develop into a noninvasive, accurate, and useful technique for assessing the retinal vasculature and comprehending the

mechanisms underlying the various pathologic changes that take place in the deep and superficial capillary plexus following treatment of Behçet's uveitis with adalimumab. Also OCTA was found to be a feasible imaging modality to monitor changes in retinal perfusion in response to treatment with adalimumab and may provide a useful marker for monitoring response to treatment.

Competing interests:

Authors have declared that no competing interests exist.

Authors' contributions:

This work was carried out in collaboration among all authors. Authors MW and MA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript.

Authors AR, AE and ME managed the analyses of the study. Author EN managed the literature searches.

All authors read and approved the final manuscript.

Consent:

All patients were informed of the nature of the study and gave written informed consent before enrollment. The study was approved by the ethics committee of university.

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دراسة التغيرات في دورة الشبكية الدموية ما بعد العلاج الحيوي باستخدام عقار اداييموماب في مرضى الالتهاب القرصي المهدد للبصير لمتلازمة بهجت

مرض بهجت يسمى أيضاً متلازمة بهجت وهو اضطراب نادر يسبب التهاب الأوعية الدموية في كل الجسم.

يمكن للمرض أن يؤدي إلى عدد من العلامات والأعراض التي قد تبدو غير مترابطة في البداية. يمكنه أن يشمل قرح الفم والتهاب في العين وطفح جلدي وأفات وقرح تناسلية.

يشمل العلاج أدوية لتخفيف علامات وأعراض مرض بهجت وللمنع المضاعفات الخطيرة مثل العمى.

وتختلف أعراض مرض بهجت من شخص إلى شخص، أو يمكن أن تظهر وتلاشى، أو تقل حدتها مع مرور الوقت. وتعتمد العلامات والأعراض على أجزاء الجسم المصابة. العينان يسبب التهاب العين الأحمر والألم والرؤية الضبابية في كلا العينين في العادة. وفي المرضى المصابين بمرض بهجت، يمكن ظهور المرض والتعافي منه.

مضاعفات مرض بهجت تعتمد على العلامات والأعراض. على سبيل المثال التهاب القرصي غير المعالج يمكنه أن يؤدي إلى تناقص في الإبصار أو العمى. لم يثبت وجود علاج أمثل في حالات الاعتلال البصري الحاد المصاحب لمرض بهجت.

يهدف العلاج الحالي إلى تقليل الأعراض، الحد من التهابات، والسيطرة على الجهاز المناعي أداييموماب هو جسم مضاد وحيد النسيلة مصدره بشري بالكامل يعد ثالث مثبّط عامل نخر الورم تم إثبات نجاحه في علاج الاعتلال القرصي الحاد الذي قد يسبب العمى في متلازمة بهجت.

في دراستنا تم إثبات تحسن الدورة الدموية ما بعد العلاج باستخدام اداييموماب مما قد يحسن الرؤية في مرضى الالتهاب القرصي لداء بهجت.