Original Article

Evaluation of the Activity of Vogt–Koyanagi–Harada Disease; A Comparison of Indocyanine Green Angiography Scoring, Enhanced Depth Imaging Optical Coherence Tomography, and Choroidal Vascularity Index

Kaveh Fadakar[1], Keivan Rezaii[1], Hanieh Niktinat[1], Ramak Roohipourmoallai[2], Tahereh Mahmoudi[3], Sonal Tuli[4], Amin Ahmadi[1], Elias Kalili Pour[1], Fatemeh Golsoorat Pahlaviani[1], Zahra Mahdizad[1], Samaneh Davoudi[5], Mohammad Zarei[1], Nazanin Ebrahimiadib[4]

[1]Department of Ophthalmology, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran, [2]Department of Ophthalmology, University of South Florida, Tampa, FL, USA, [3]Department of Medical Physics and Biomedical Engineering, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran, [4]Department of Ophthalmology, University of Florida, Gainesville, FL, USA, [5]Department of Ophthalmology, Boston Medical Center, Boston, MA, USA

Abstract

Purpose: To investigate the correlation between choroidal biomarkers using enhanced depth imaging optical coherence tomography (EDI-OCT) and indocyanine green angiography (ICGA) scoring for monitoring the activity of Vogt–Koyanagi–Harada (VKH).

Methods: Patients who were not in the acute phase of VKH were recruited. Simultaneous EDI-OCT and ICGA were captured in seven patients only at baseline, in six patients at the 3-month follow-up, and in two patients at both the 6- and 9-month follow-ups. Subfoveal choroidal thickness (SFCT), subfoveal choroidal area (SFCA), and choroidal vascular index (CVI) were measured on EDI-OCT using FIJI software and a denoising system. ICGA scoring was performed.

Results: Fifteen subjects with the median of 4-month follow-up were recruited. Forty-eight pairs of EDI-OCT and ICGA were investigated. In univariate analysis, ICGA scores were positively associated with SFCT, and SFCA, but negatively with CVI. The strength of correlation between ICGA scores and SFCT was strong (correlation coefficient: 0.91). In multivariate analysis, only SFCT remained significant (B: 2.4, 95% confidence interval: 1.9–3.0; $P < 0.001$).

Conclusions: SFCT can be an acceptable representative of the subclinical inflammatory activity of VKH. As an alternative to ICGA, SFCT functions better than SFCA and CVI.

Keywords: Choroidal vascular index, Enhanced depth imaging optical coherence tomography, Indocyanine green angiography, Subfoveal choroidal area, Subfoveal choroidal thickness, Vogt–Koyanagi–Harada

Address for correspondence: Nazanin Ebrahimiadib, University of Florida, Gainesville, FL, USA.
E-mail: nebrahimiadib@ufl.edu
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Introduction

Vogt–Koyanagi–Harada (VKH) is an autoimmune inflammatory syndrome mediated by T-cell lymphocytes targeting melanocytes in the eyes, ears, nervous system, and skin. The classic ocular presentation of VKH is bilateral granulomatous panuveitis with diffuse choroiditis.[1] The inflammation involves stromal choroidal vessels in both Haller and Sattler layers

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and is associated with subretinal exudate and bullous retinal detachments.[2]

Acute VKH manifests with multifocal exudative retinal detachment with dramatic decline in vision. This phase should be treated with a combination of corticosteroid and immunomodulatory therapy within 1 month of initiation. If not properly treated, it becomes chronic with choroidal thinning and scar and possible recurrence. This chronic phase is associated with sunset-glow fundus and poor visual outcomes.[3] Therefore, detection and treatment of any subclinical inflammation are important to avoid sight-threatening complications.[4] For this purpose, the choroidal inflammation should be regularly monitored with ocular imaging, as it cannot be reliably detected by clinical presentations alone.[5] Indocyanine green angiography (ICGA) is known to be the gold standard test for detecting any level of disease activity even when the fundoscopic examination and fluorescein angiography (FA) are unremarkable. The main findings of VKH disease in ICGA are hyperfluorescence and leakage of choroidal vessels, fuzzy choroidal vascular pattern, hypofluorescent dark dots (HDDs), and hyperfluorescence of optic disc. However, ICGA is an invasive test and may not be available in every center.

More recent technologies in ocular imaging showed promise in early diagnosis and treatment monitoring of VKH. These include swept-source optical coherence tomography (OCT) and enhanced depth imaging optical coherence tomography (EDI-OCT) which enable evaluation of the choroidal thickness in the course of the disease.[6,7] However, some researchers argued that EDI-OCT may not be as accurate as ICGA for detecting the activity of VKH, given that OCT mainly illustrates macula while VKH is a panfundus pathology.[8] Choroidal vascular index (CVI) is another recently introduced biomarker in choroidal pathology that has some role in monitoring disease progression in VKH.[9] However, few studies compared ICGA with EDI-OCT in different stages of VKH, and no study compared these with CVI.

In this study, we aim to investigate the correlation of choroidal biomarkers, including subfoveal choroidal thickness (SFCT), choroidal area, and CVI obtained from EDI-OCT and compare them with ICGA scoring to determine the potential of EDI-OCT as an alternative to ICGA to assess disease activity and adjust the treatment plan.

Methods

The present study is an observational case series conducted in a referral uveitis clinic. We enrolled sequentially from March 2020 to February 2022, individuals who were diagnosed with VKH disease, according to the Revised Diagnostic Criteria Proposed by the International Nomenclature Committee Diagnostic Criteria for VKH disease.[2,10] Inclusion criteria consisted of patients with ongoing inflammation activity of VKH under one of these circumstances: (1) acute phase remission of VKH defined as the earliest time after resolution of exudative retinal detachment when there is no more subretinal fluid and choroidal vascular structure is restoring in EDI-OCT or (2) chronic recurrent phase defined as patients with typical features of choroidal thinning or ocular depigmentation, while there is still signs of disease activity in examination or ICGA. Choroidal vasculature structure restoring was defined as the relative reestablishment of the details of choroidal vascular layers in contrast to indistinct vascular structure in the acute phase of the disease.

Oral and written informed consent were obtained from participants before their enrolment into the study. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Tehran University of Medical Sciences' Institutional Review Board (Ethic code: IR.TUMS.FARABIH.REC.1397.045).

Patients were treated with simultaneous steroids (initial high dose with very slow tapering) and immunomodulatory therapy upon diagnosis was established. After the clinical resolution of the acute phase, steroid tapering and judicious adjustment of immunomodulation were ensued. Baseline demographic characteristics including age, sex, past medical, and drug history were recorded at the initial visit. All patients underwent complete ophthalmic evaluation including refraction and measurement of best-corrected visual acuity using Snellen charts, slit-lamp biomicroscopy, applanation tonometry, and dilated fundus examination. Patients with refractive error of $\geq\pm3$ and axial length of <21 mm or >25 mm were excluded. In addition, patients with other concomitant retinal pathologies such as previous history of glaucoma, panuveitis compatible with other inflammatory entities such as ocular tuberculosis, those with history of ocular trauma, and intraocular surgery were excluded.

We performed FA, EDI-OCT, and ICGA for all included patients, at the beginning within 1 month of complete subretinal fluid absorption. In subsequent follow-up visits at 3, 6, and 9 months, data of simultaneous EDI-OCT and ICGA were assessed, if available.

EDI-OCT was performed using Heidelberg Spectralis OCT (Heidelberg Engineering Inc., Heidelberg, Germany). All EDI-OCT images were performed between 9 and 12 AM. A 5 mm × 5 mm image centered at fovea was obtained for each eye and the choroidal thickness was measured with 25 EDI scans in the macular area or subfovea. A public domain software (available in the public domain at Fiji; http://imagej.nih.gov/ij) was used to analyze the images. The scan which passes through the foveal center was selected for image analysis. Images with low quality, in which the choroidoscleral junction was not recognizable were omitted. Following the adjustment of the image scale, the SFCT was defined as the vertical distance between two hyperreflective boundaries: the RPE-Bruch's membrane and the sclerochoroidal interface [Figure 1].

Using the polygonal selection of the software, the total subfoveal choroidal area (SFCA) was selected from the most

nasal up to 8 mm temporally. The selected area was indexed as the region of interest (ROI), using the ROI manager tool of the software. EDI-OCT images, due to the internal physics of the method, suffer from speckle noise, especially in cases of VKH syndrome with increased choroidal thickness and concomitant inflammation. Therefore, to reduce the speckle noise, we applied a denoising method based on sparse dictionary learning.[11] Binarization and segmentation of OCT images were performed using modified protocol described by Sonoda *et al*.[12] In brief, images were converted from red, green, and blue (RGB) to 8-bit. Using the ROI manager tool of the software, the area was added as ROI. Niblack's auto-thresholding method was used for binarization to delineate stromal and luminal areas. Total SFCA was retrieved as ROI and calculated using measure tool [Figure 1a and b]. The image was then converted to RGB and color channels were restored. CVI is defined as the proportion of vascular luminal area with bright pixels to total choroidal area [Figure 1c and d]. All OCT measurements were performed by an expert (AA) who was blind to the clinical data and other imaging modalities of the patients.

Heidelberg Retina Angiograph (HRA-2) (Heidelberg Engineering Inc., Heidelberg, Germany) was used for image acquisition. After a bolus injection of 8 mg of indocyanine green (ICG) diluted in 1 ml of distilled water, early frames of angiograms were taken from the posterior pole after approximately 2–3 min. The intermediate phase was obtained at 12 ± 3 min after ICG injection by collecting frames of the posterior pole and a minimum of eight frames of the entire 360° periphery. The late ICGA frames were captured at 30–40 min after ICG injection in the same fashion as for the intermediate phase.

ICGA images were graded using a well-established highly reproducible scoring system ranging from 0 to 20. Briefly, scores were assigned to specific ICGA signs based on their intensity and extension throughout the posterior pole and other quadrants. The ICGA signs were early stromal vessel hyperfluorescence at 0–5 min [Figure 2a and b], choroidal vasculitis at 10–20 min described as fuzzy vessels with indistinct course [Figure 2c], HDD at posterior pole or each of four quadrants [Figure 2d], and finally, optic disc hyperfluorescence after 15 min. ICGA scoring was performed by two uveitis experts.[13] The experts were blind to the clinical data and other imaging modalities of the patient. Representative ICGA signs are illustrated in Figure 2.

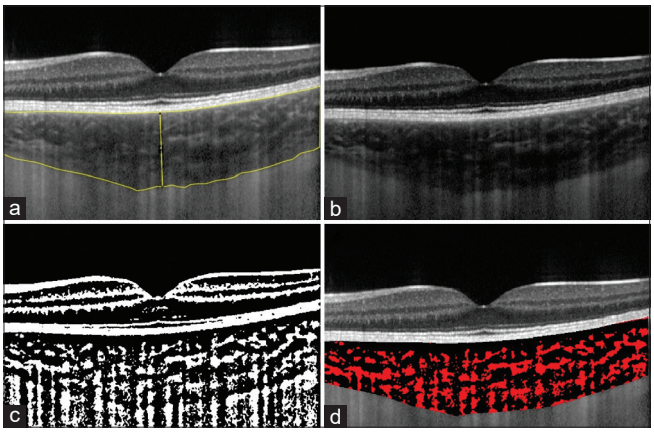

Figure 1: Representative enhanced depth imaging optical coherence tomography processing. Subfoveal choroidal thickness was measured as the line below RPE to choroidoscleral junction at subfovea. Choroidal area was measured using polygonal detection tool (a). Sparse representation denoising was applied (b), followed by binarization (c). The ratio of vascular lumen to subfoveal choroidal area is choroidal vascular index (d)

Statistical analysis

Data are presented as mean ± standard deviation for quantitative values. Intraclass correlation coefficient (ICC) was applied to determine inter-rater reliability of ICGA grading. To compensate for repeated measurements and the inclusion of both eyes of the patients in the study, linear mixed model was used to evaluate the association of ICG scoring with EDI-OCT parameters. Partial correlation analysis was performed to demonstrate the strength of the association between ICGA score and EDI-OCT parameters. Data were analyzed by SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA: IBM Corp). P <0.05 level was considered significant.

Results

A total of 30 eyes of 15 patients met the inclusion criteria. Five patients (33%) were female and the mean age was

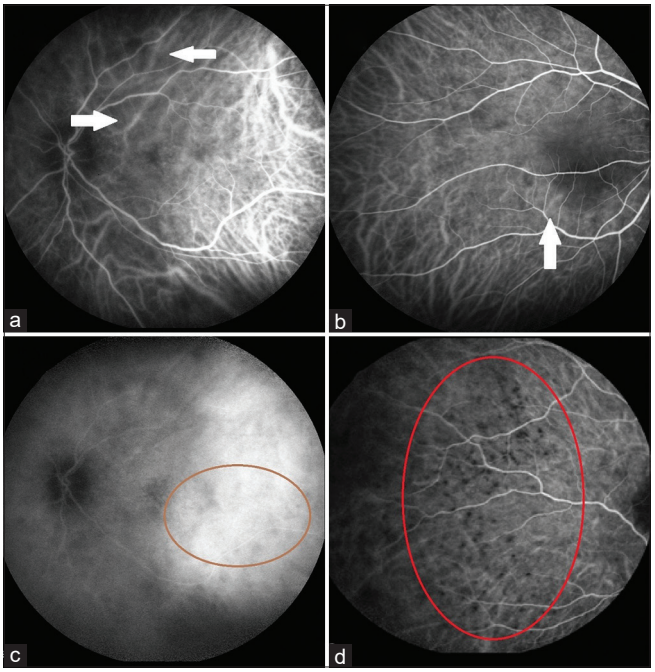

Figure 2: Representative indocyanine green angiography signs for grading. White arrows indicate early stromal choroidal vessel hyperfluorescence in posterior pole (a) and temporal macula (b). An area with fuzzy vessels without any recognizable course is encircled (c). Multiple hypofluorescent dark dots are circumscribed by an oval (d)

26 ± 11 (range, 12–50) years. Table 1 demonstrates the baseline characteristics of the participants.

Overall, 48 pairs of ICGA and EDI-OCT images, performed in four different sessions during the follow-up period, were evaluated. Seven patients did not have follow-up, and only baseline EDI-OCT and ICGA images were analyzed. Six patients had images at 3-month follow-up, and two patients had follow-ups at 3 and 6 and 9 months (Supplementary Table 1). ICC agreement between two raters for ICGA images was 0.90 (95% confidence interval [CI]: 0.68–0.97).

The mean choroidal thickness at baseline was 366 ± 99 µm, at 3-month follow-up was 401 ± 67 µm, at 6 months was 342 ± 28 µm, and at 9-month follow-up was 388 ± 72 µm. Pairwise comparison revealed that the difference between 3rd month and 6th month was statistically significant (P = 0.035). The mean choroidal area at baseline, 3 months, 6 months, and last follow-up was 0.70 ± 0.26, 0.81 ± 0.55, 0.61 ± 0.11, and 0.66 ± 0.22; respectively. CVI at baseline was 66.12 ± 4.01, at month 3 was 67.51 ± 3.10, at month 6 was 66.28 ± 3.15, and at month 9 was 66.17 ± 0.60. The mean ICGA score was 6.55 ± 2.62 at the baseline, 7.54 ± 2.67 at 3 months, 7.00 ± 1.41 at 6 months, and 8.75 ± 3.18 at the last examination. Table 2 shows the alterations of OCT biomarkers during follow-up.

Linear mixed model analysis showed that there is a statistically significant relation between SFCT and ICGA scoring during the study courses; with each 100 µm increase in SFCT, 2.6 increase was observed in ICGA score (95% CI: 2.3–2.9, P < 0.001) [Figure 3]. Choroidal area was also associated with ICGA scoring (B: 1.74, 95% CI: 0.13–3.35; P = 0.034) [Figure 3]. A significant negative association was observed between CVI and ICGA scores. Every one score increase in ICGA was associated with 0.23 decrease in CVI (95% CI: −0.44– −0.02; P = 0.031) [Figure 3].

To evaluate the strength of correlation, partial correlation analysis, controlling for the effect of repeated measurements, was applied. Accordingly, a significant positive strong association was observed between SFCT and ICGA scores (correlation coefficient: 0.91, P < 0.001). A negative significant, but relatively weak association was observed between CVI and ICGA score (correlation coefficient: −0.40, P = 0.011). In contrast, choroidal area revealed a weak but positive association with ICGA scoring (correlation coefficient: 0.39, P = 0.009).

Multivariate linear mixed model analysis, choroidal thickness, choroidal area, and CVI were performed to determine the independent predictor of ICG score. Only choroidal thickness was significantly associated with ICG score (B: 2.4, 95% CI: 1.9–3.0; P < 0.001). The relation of choroidal area (B: 0.61, 95% CI: −0.57–1.81; P = 0.300) and CVI (B: 0.01, −0.11–0.13; P = 0.853) with ICGA score was not significant in multivariate analysis.

Table 1: Baseline characteristics of the participants

Variables	Values
Age (years)	26±11 (12–50)
Gender, *n* (%)	
Male	10 (66.7)
Female	5 (33.3)
BCVA (logMAR)	0.20±0.26 (0–0.7)
SE (diopter)	−0.50±1.68 (−2.25–1.75)
Disease status, *n* (%)	
Chronic recurrent	8 (26.6)
Postacute phase remission	22 (73.3)

BCVA: Best-corrected visual acuity, SE: Spherical equivalent

Table 2: Alterations of enhanced depth imaging optical coherence tomography biomarkers and indocyanine green angiography scoring during time

Variables	Baseline	Months 3	Months 6	Months 9	*P*
Number of patients	15	6	2		
SFCT (µm)	366±99	401±67	342±28	388±72	0.050
Choroidal area (mm^2)	0.70±0.26	0.81±0.55	0.61±0.11	0.66±0.22	0.071
CVI	66.12±4.01	67.51±3.10	66.28±3.15	66.17±0.60	0.701
ICGA scoring	6.55±2.62	7.54±2.67	7.00±1.41	8.75±3.18	0.389

SFCT: Subfoveal choroidal thickness, CVI: Choroidal vascular index, ICGA: Indocyanine green angiography

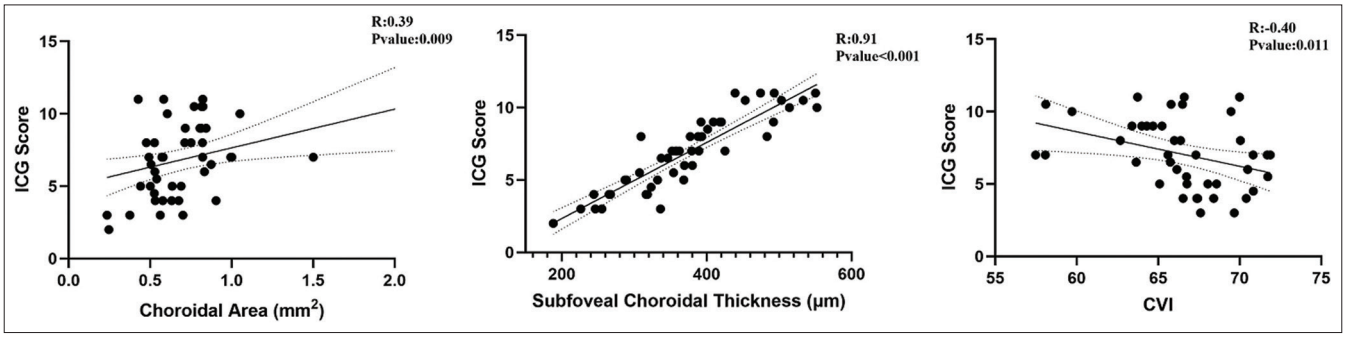

Figure 3: Association of enhanced depth imaging optical coherence tomography biomarkers with indocyanine green angiography (ICGA) scoring. Subfoveal choroidal thickness had a significant strong positive correlation with ICGA scoring, while association with choroidal area was moderate. Choroidal vascular index had significant moderate negative association with ICGA scoring

Discussion

ICGA is the gold standard modality for monitoring disease activity in the course of VKH. The ideal schedule includes performing ICGA every 5–6 weeks in the first 4–5 months of treatment and then every 2–3 months.[3] However, it is invasive, time-consuming, and expensive. EDI-OCT is a more accessible and noninvasive imaging modality that yields valuable information regarding choroidal structure. In this study, we assessed the predictability of ICGA scores by EDI-OCT choroidal biomarkers. Based on our findings, SFCT was the biomarker that showed strong association with ICGA scores. SFCA and CVI were moderately correlated and failed to prove significance in multivariate analysis. SFCT remained to be the sole predictor of ICGA scores and can be considered an alternative to ICGA to monitor the inflammatory activity of VKH.

It is known that when the acute phase of VKH disease subsides, choroidal thickness dramatically decreased, but it will not become completely normal for months to years, indicating smoldering inflammatory activity of the disease.[14-17]

We evaluated the correlation of OCT and ICGA in both postacute remission and chronic recurrent phase of VKH disease [Supplementary Table 2]. In an investigation on eyes in the chronic stage of VKH using a simplified four-score grading of ICGA, Jap and Chee showed an association between ICGA scoring and SFCT. Despite our results, their finding was evident for a moderate-to-weak correlation (Spearman's *r*: 0.49). The relative discrepancy may be attributed to different scoring systems for ICGA and different stages of disease activity which affects choroidal thickness. In fact, the average SFCT in our patients was higher than in the mentioned study.[6]

In accordance with our result, some evidence indicates that even in the chronic phase of the VKH, when the choroid becomes thin, choroidal thickness is positively correlated with posterior and/or anterior recurrence of inflammation.[7,18-22] It is noteworthy that in the chronic phase of VKH, Dalen–Fuchs-like scars and pigmentations and fibrosis may be mistaken for HDDs, as all appear dark in ICGA and confirmation with fundus photo is crucial in this phase to avoid overdiagnosis of disease activity. Interestingly, EDI-OCT does not have such limitations, and measurement of choroidal thickness is more straightforward.

In univariate analysis, SFCA showed a positive association, while CVI showed a negative correlation with disease activity. This is in accordance with histologic interpretation of VKH, as enhancement of the choroidal area is mainly due to enlargement of the stromal component of the choroid rather than vascular lumen dilation. However, other studies evaluating CVI during the course of VKH yielded conflicting results. Kawano *et al*. demonstrated an increase in CVI after treatment,[23] and Agrawal *et al*. and Jaisankar *et al*. showed a decline in CVI, following treatment.[9,24] The discrepancy among these studies indicates that this index may not be a reliable one for the evaluation of VKH activity. CVI even has a narrow window between a normal and diseased condition.[25] One reason for these conflicting results may be due to the high level of noise which is an inherent drawback for this measurement, especially in the inflammatory condition with thick choroid. Due to this limitation, we employed a denoising technique before the CVI calculation which consolidated our results. Despite these measures, multivariate analysis failed to show an independent role for CVI in evaluating VKH activity. It seems that SFCT is dominating the alteration of SFCA and CVI with ICGA scores.

Of note, our study has some limitations. Small sample size is one of them. In addition, choroid thickness may vary with age, sex, and axial length which is not controlled in this study. Another limitation of this study is that the patient may not be at the same stage of evolution. Due to the variable number of cases in each interval of follow-up, longitudinal analysis to account for the duration of the disease was not possible. Further larger studies are necessary to verify our results.

In conclusion, the evaluation of SFCT can be considered an alternative to ICGA scoring during the assessment of VKH inflammatory activity. Choroidal area in the posterior pole and CVI did not show significant value in multivariate analysis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Individual measurements of subfoveal choroidal thickness and indocyanine green score of each participant during the follow-up

	SFCT (μm)	ICG score
Patient 1		
Baseline		
OD	393	8
OS	265	4
3 months		
OD	336	3
OS	354	5
6 months		
OD	377	8
OS	332	5
9 months		
OD	337	6.5
Patient 2		
Baseline		
OD	287	5
OS	318	4
3 months		
OD	388	8
OS	493	11
Patient 3		
Baseline		
OD	358	7
OS	323	4
3 months		
OD	380	6
OS	267	4
6 months		
OD	309	8
OS	352	7
9 months		
OD	439	11
Patient 4		
Baseline		
OD	316	4
OS	244	4
Patient 5		
Baseline		
OD	425	7
OS	389	7
3 month		
OS	369	6
Patient 6		
Baseline		
OD	552	10
OS	533	10.5
3 months		
OD	453	10.5
Patient 7		
Baseline		
OD	362	7
OS	346	6.5
Patient 8		
Baseline		
OD	492	9
OS	392	9
3 months		
OD	483	8
Patient 9		
Baseline		
OD	357	7
OS	503	10.5
Patient 10		
Baseline		
OD	418	9
OS	409	9
3 months		
OS	401	8.5
Patient 11		
Baseline		
OD	289	5
OS	226	3
3 months		
OD	420	9
OS	474	11
Patient 12		
Baseline		
OD	368	5
OS	379	7
Patient 13		
Baseline		
OD	550	11
OS	514	10
Patient 14		
Baseline		
OD	246	3
OS	188	2
Patient 15		
Baseline		
OD	255	3
OS	307	5.5

SFCT: Subfoveal choroidal thickness, ICG: Indocyanine green, OD: Right eye, OS: Left eye

Supplementary Table 2: Comparison of the optical coherence tomography biomarkers and indocyanine green angiography scores in eyes with chronic recurrent and in remission

Variables	Remission	Chronic recurrent	*P*
SFCT (μm)	375±100	375±75	0.568
Choroidal area (mm^2)	0.68±0.19	0.79±0.50	<0.001
CVI	65.87±3.23	66.51±4.26	<0.001
ICGA scoring	6.85±2.86	7.15±2.28	0.580

Enhanced depth imaging OCT. SFCT: Subfoveal choroidal thickness, CVI: Choroidal vascular index, ICGA: Indocyanine green angiography, OCT: Optical coherence tomography