Changes in choroidal imaging parameters following adalimumab therapy for refractory noninfectious uveitis

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Title: Changes in choroidal imaging parameters following adalimumab therapy for refractory non-infectious uveitis

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Key messages:

The efficacy of adalimumab in patients with noninfectious intermediate, posterior and panuveitis (NIPPU) has been assessed based on clinical findings obtained by conventional biomicroscopy. In this study, we utilised enhanced depth imaging optical coherence tomography (EDI-OCT) and attempted to investigate whether choroidal imaging parameters obtained by EDI-OCT are helpful in monitoring disease activity following the initiation of adalimumab therapy in eyes with refractory NIPPU. Our data indicates that the efficacy of adalimumab therapy could be better monitored by subfoveal choroidal thickness than the choroidal stromal index defined as the proportion of stromal area to the total choroidal area stromal area. From the results of subgroup analysis, Vogt-Koyanagi-Harada disease is likely to be most suitable for EDI-OCT evaluation.

Abstract

Purpose: To evaluate the short-term change in choroidal structure following adalimumab (ADA) treatment in refractory non-infectious uveitis.

Methods: This was a retrospective study of 33 eyes from 18 patients with refractory non-infectious uveitis. Subfoveal choroidal thickness (SFCT), the choroidal stromal index (CSI) defined as the proportion of stromal area to the total choroidal area were used as choroidal imaging parameters, and were evaluated by enhanced depth imaging optical coherence tomography (EDI-OCT). The change in these parameters in the 2 months following initiation of ADA were analysed. A linear mixed-effect model was used to assess the effect of ADA treatment.

Results: The causes of uveitis were Vogt-Koyanagi-Harada disease (VKHD) (42.4%), presumed autoimmune retinopathy (15.2%), others (12.1%), and unclassified (30.3%). In the analysis of all eyes, the SFCT was 309.7 ± 113.1 μm at baseline, 295.7 ± 114.5 μm at 1 month, and 275.2 ± 98.8 μm at 2 months after ADA initiation ($P < 0.001$). The CSI was 0.275 ± 0.050 at baseline, 0.273 ± 0.068 at 1 month, and 0.273 ± 0.046 at 2 months ($P = 0.785$). In the subgroup analysis, the SFCT decreased significantly from baseline to 2 months in VKHD eyes ($P = 0.007$) and unclassified eyes ($P = 0.034$). There was no significant change in CSI in either subgroup.

Conclusions: In the assessment of short-term response to ADA treatment in uveitic eyes, using EDI-OCT, the SFCT appears to be more effective as a choroidal imaging biomarker than the CSI, especially in VKHD eyes.

Keywords: noninfectious uveitis; Vogt-Koyanagi-Harada disease; adalimumab; optical coherence tomography; subfoveal choroidal thickness; choroidal stromal index

INTRODUCTION

Adalimumab (Humira; AbbVie Inc, North Chicago, IL), a recombinant human IgG1 monoclonal antibody specific for human TNF-α, was approved by the US Food and Drug Administration as the first noncorticosteroid medication for the treatment of non-infectious intermediate, posterior, and panuveitis (NIPPU) in 2016. However, its efficacy in a real-world clinical setting has remained a concern for uveitis specialists who care for patients suffering from refractory NIPPU. Level 1 evidence on the efficacy of adalimumab in patients with active or inactive NIPPU originates from VISUAL studies (VISUAL I and II), in which the primary efficacy endpoint was time to treatment failure, based on clinical findings obtained by biomicroscopy and best-corrected visual acuity [1,2]. The VISUAL III study was a multicentre open-label study to evaluate the long-term efficacy and safety of adalimumab in patients with NIPPU. The main outcome measure of the VISUAL III study was quiescence of inflammation, defined using biomicroscopic findings: no active inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber cell grade ≤ 0.5+, and vitreous haze grade ≤ 0.5+ in both eyes [3]. Biomicroscopic findings have been the gold standard to measure the degree of intraocular inflammation [4]. However, recent advances in non-invasive ocular imaging in clinical ophthalmology has enabled objective and quantitative measurement of ocular tissues, and most of these imaging modalities can detect even small changes that traditional biomicroscopy cannot [5]. Accordingly, if non-invasive ocular imaging modalities were to be used in the assessment of ocular inflammation, the efficacy of adalimumab on NIPPU activity could be monitored accurately.

The choroid of the eye is a highly vascularised structure extending from the optic nerve head to the ora serrata, and represents one of the most common sites of ocular inflammation [6,7]. Histologically, the choroid can be divided into several layers (i.e., Bruch's membrane, the choriocapillaris, Haller's and Sattler's layers, and the suprachoroid) [6], and enhanced depth imaging optical coherence tomography (EDI-OCT) can successfully and noninvasively depict these choroidal layers [8,9]. As a result, signs obtained by EDI-OCT are

commonly utilised as a diagnostic aid and/or a parameter for disease monitoring in uveitic eyes [5,7]. Of the numerous choroidal OCT parameters, subfoveal choroidal thickness (SFCT) and indexes generated from the luminal and stromal areas of the choroid are perhaps the best studied, and are frequently used as choroidal biomarkers [10-17].

In this study, we examined the eyes of patients with NIPPU who had been treated with adalimumab, and evaluated the impact of the treatment on choroidal OCT parameters in order to determine whether choroidal OCT parameters are of use in monitoring disease activity after the initiation of adalimumab therapy.

MATERIALS AND METHODS

Study design and inclusion/exclusion criteria

This was a retrospective chart review of 33 eyes from 18 patients who received adalimumab therapy for refractory NIPPU at Kobe University Hospital, Kobe, Japan. The study adhered to the tenets of the Declaration of Helsinki, and The Institutional Review Board of Kobe University Graduate School of Medicine granted approval for this study; the requirement for informed consent was waived due to the retrospective nature of the study. Clinical data were extracted from the patients' medical records, and included the following: age, sex, affected eye, type and cause of uveitis, duration of uveitis, best-corrected visual acuity (BCVA), intraocular pressure, lens status, axial length, estimated glomerular filtration rate, previous treatment for uveitis, concomitant use of corticosteroids and/or other immunomodulators, intraocular inflammation, OCT parameters described below and adverse events. This study included patients who were diagnosed with NIPPU, whose uveitis was uncontrolled with conventional immunomodulatory therapy, who were treated with adalimumab therapy between November 2016 and February 2020, and who were followed up for at least 2 months after the initiation of adalimumab therapy. The cause of uveitis was determined based on the diagnostic criteria [18-21]. Eyes with presumed autoimmune retinopathy (PAIR) were determined as those that met the diagnostic criteria for autoimmune retinopathy [22], but

the patients were not tested for serum antiretinal antibodies. Patients were excluded if they met one of the following criteria: (1) severe media opacities that could affect the quality of OCT images; (2) any ocular pathology, except for NIPPU, that may affect retinal and/or choroidal status; and (3) severe renal dysfunction.

Treatment and outcome variables

At the initiation of adalimumab therapy, patients received a loading dose of 80 mg subcutaneous adalimumab injection, followed by 40 mg every other week, starting 1 week after the initial dose. Patients were permitted to have concomitant immunosuppressive therapy (such as oral corticosteroids or cyclosporine). Rheumatologists assessed the risk for infection, demyelinating disease, and malignancy before the initiation of adalimumab, and monitored thereafter.

The main outcome measures were change in subfoveal choroidal thickness (SFCT) and choroidal stromal index (CSI), determined by EDI-OCT from baseline (adalimumab onset) to 2 months after adalimumab initiation. The SFCT and CSI were determined as follows. Horizontal cross-sectional EDI-OCT images passing through the fovea were acquired using spectral domain optical coherence tomography (SD-OCT, Spectralis; Heidelberg Engineering, Heidelberg, Germany). SFCT was defined as the vertical distance from the outer border of the hyperreflective retinal pigment epithelium (RPE) to the choroid-sclera interface at the fovea. CSI calculation was performed by referring to previous works using ImageJ software (ImageJ version 1.51, National Institutes of Health; Bethesda, Maryland, USA) [23]. The region of interest (ROI) was determined, and selected on each grayscale EDI-OCT image. The upper and lower border of the ROI was the outer border of the RPE line and the choroid-sclera interface, respectively. The nasal and temporal border was a line drawn perpendicular to the RPE line 1,500 μm nasally or temporally away from the centre of the fovea. Next, the average OCT signal value of three randomly selected choroidal vessels (length of major axis > 100 μm) was calculated by the software. The average value was set as the minimum value to minimise noise in the OCT image. Then, the image was converted to 8 bits and adjusted by

148 the auto local threshold of Niblack. The binarised image was reconverted to an RGB image,
149 and the luminal area was determined using the threshold tool. After the data for the distance
150 of each pixel were added, the total choroid area, luminal area (the black pixels) and stromal
151 area (the light pixels) of the ROI were automatically calculated. The CSI was defined as the
152 ratio of the stromal area to the total choroid area (Figure 1).
153 The BCVA was measured using a Landolt C chart, and IOP measurement was taken
154 by a Goldmann applanation tonometer or noncontact tonometer (FT-1000, TOMEY; Japan).
155 The axial length was measured using an IOL master (model 500, Carl Zeiss, Germany).
156 Evaluation of intraocular inflammation was performed according to the National Eye
157 Institute criteria adapted by the Standardisation of Uveitis Nomenclature Working Group, in
158 order to obtain values of cells and flare in the anterior chamber and vitreous haze [24,4].
159 Information on systemic adverse events was collected from the patients' medical record. The
160 secondary outcome measures were change in anterior chamber cell, anterior chamber flare
161 and vitreous haze from baseline to 2 months after adalimumab initiation.
162 **Statistical analyses**
163 Numerical data are provided as mean ± standard deviation unless otherwise specified.
164 Decimal BCVAs were converted to the logarithm of the minimum angle of resolution
165 (logMAR) equivalent for statistical analyses. Statistical analyses were performed using SPSS
166 software version 24.0 (SPSS Inc, Chicago, IL). Linear mixed-effect model analysis was used
167 to assess the change in variables over time. $P < 0.05$ (two-sided) was accepted as statistically
168 significant in each analysis.
169
170 **RESULTS**
171 The data on 33 eyes from 18 patients who met the abovementioned criteria were analysed.
172 The patients' characteristics at baseline are shown in Table 1. Of the 18 patients, 12 (66.7%)
173 were female, 15 (83.3%) had bilateral uveitis, and both eyes were similarly included for
174 analyses: 18 (54.5%) right eyes and 15 (45.5%) left eyes. Regarding lens status, 17 (51.5%)

175 eyes were phakic and 16 (48.5%) eyes were pseudophakic. The mean axial length, logMAR
176 BCVA and IOP were 23.50 ± 1.21 mm, 0.133 ± 0.412, and 16.4 ± 16.7 mmHg, respectively.
177 The eyes were diagnosed with Vogt-Koyanagi-Harada disease (VKHD), PAIR (1 patient had a
178 history of breast cancer), sarcoidosis, or Behçet's disease. Ten eyes that did not meet any
179 diagnostic criteria were categorised as unclassified. Prior to adalimumab administration, the
180 included patients had been suffering from recurrent intraocular inflammation, visual field
181 deterioration due to progressive outer retinal damage, or side effects of corticosteroid
182 therapy. A total of 15 (83.3%) patients were treated with adalimumab monotherapy, and 3
183 (16.7%) patients were treated with a combination therapy of adalimumab and cyclosporin.
184 Systemic corticosteroids were administrated in 9 (50%) patients at the start of adalimumab
185 which were tapered following the initiation of adalimumab therapy in all cases.
186 In the analysis of all eyes after the initiation of adalimumab therapy, the mean SFCT
187 significantly decreased from baseline to 2 months (309.7 ± 113.1 μm at baseline, 295.7 ±
188 114.5 μm at 1 month, and 275.2 ± 98.8 μm at 2 months; P = 0.002) (Figure 2A). The mean
189 CSI showed no significant decrease in the 2 months following adalimumab administration
190 (0.275 ± 0.050 at baseline, 0.273 ± 0.068 at 1 month, and 0.273 ± 0.046 at 2 months; P =
191 0.862) (Figure 2B). There was no significant change in anterior chamber cell, anterior
192 chamber flare and vitreous haze from baseline to 2 months after adalimumab initiation. The
193 mean anterior chamber cell score was 0.2 ± 0.4 at baseline, 0.1 ± 0.4 at 1 month, and 0.1 ±
194 0.3 at 2 months (P = 0.211). The mean anterior chamber flare score was 0.0 ± 0.2 at baseline,
195 0.0 ± 0.0 at 1 month, and 0.0 ± 0.0 at 2 months (P value was not obtained). The mean
196 vitreous haze score was 0.3 ± 0.6 at baseline, 0.2 ± 0.4 at 1 month, and 0.3 ± 0.50 at 2
197 months (P = 0.678). No systemic adverse events were noted in the 2 months following the
198 initiation of adalimumab therapy.
199 The effect of the cause of uveitis on changes in the SFCT or CSI was also examined.
200 The eyes were classified into four groups as follows: VKHD, PAIR, others (sarcoidosis or
201 Behçet's disease), and unclassified. The mean SFCT after adalimumab initiation was 385.8 ±

109.6 μm at baseline, 351.4 ± 116.6 μm at 1 month, and 333.5 ± 102.4 μm at 2 months in VKHD (P = 0.007); 253.6 ± 72.0 μm at baseline, 214.0 ± 87.3 μm at 1 month, and 246.2 ± 76.9 μm at 2 months in PAIR (P = 0.141); 210.0 ± 63.1 μm at baseline, 212.0 ± 87.3 μm at 1 month, and 259.7 ± 76.9 μm at 2 months in others (P value was not obtained due to a Hessian matrix error); and 271.1 ± 87.7 μm at baseline, 270.6 ± 96.0 μm at 1 month, and 197.0 ± 54.7 μm at 2 months in unclassified (P = 0.034) (Figure 2C). The mean CSI after the commencement of adalimumab therapy was 0.247 ± 0.054 at baseline, 0.237 ± 0.063 at 1 month, and 0.250 ± 0.052 at 2 months in VKHD (P = 0.756); 0.314 ± 0.021 at baseline, 0.309 ± 0.028 at 1 month, and 0.312 ± 0.028 at 2 months in PAIR (P value was not obtained due to a Hessian matrix error); 0.252 ± 0.029 at baseline, 0.270 ± 0.040 at 1 month, and 0.285 ± 0.029 at 2 months in others (P value was not obtained due to a Hessian matrix error); and 0.302 ± 0.032 at baseline, 0.321 ± 0.068 at 1 month, and 0.286 ± 0.025 at 2 months in unclassified (P = 0.088) (Figure 2D). OCT images from a representative case of each group are shown in Figure 3.

DISCUSSION

In the current study, we evaluated the impact of adalimumab therapy on choroidal structure in eyes with refractory NIPPU, with the aim to test the usefulness of two OCT-based choroidal parameters (i.e., SFCT and CSI) as clinical biomarkers. Although CSI remained nearly unchanged after adalimumab therapy, SFCT steadily decreased in the 2 months after adalimumab initiation.

In Japan, although adalimumab was approved in September 2016 for the treatment of non-infectious intermediate uveitis, posterior uveitis or panuveitis, its use has been limited to patients who have had an inadequate response to conventional therapies. In addition, the incidence and prevalence of uveitis differs enormously across the world [25]. Therefore, these two factors would have strongly affected the distribution of the cause of uveitis in this study. The global multicentre study VISUAL III, enrolled patients with active

229 or inactive NIPPU and therefore included patients whose intraocular inflammation was
230 quiescent before adalimumab therapy. The primary cause of uveitis in VISUAL III was
231 idiopathic (33%), followed by VKHD (19%), sarcoidosis (14%), and Behçet's disease (14%) [3].
232 In contrast, Al-Janabi et al. conducted a retrospective study to examine the effect of biologic
233 agents for patients with NIPPU refractory to treatment with corticosteroids and
234 immunosuppressive drugs in the United Kingdom. In their cohort, the causes of uveitis were
235 Behçet's disease (32.7%), idiopathic (21.8%), and HLA-B27-related uveitis (16.0%), while
236 VKHD only accounted for 3.8% [26]. In our study, the main cause of uveitis was VKHD
237 (42.4%), followed by unclassified (or idiopathic) (24.2%) and PAIR (15.2%).
238 Choroidal thickness is one of the most studied choroidal metrics, and choroidal
239 thickness at the fovea, SFCT, has been frequently used as an outcome in various clinical
240 studies [27]. A recent report showed a 11.54% decrease in SFCT 12 months after the
241 initiation of adalimumab therapy for refractory noninfectious uveitis [28]. In our study, the
242 mean SFCT significantly decreased from baseline to 2 months after adalimumab therapy, and
243 subsequent subgroup analysis demonstrated that the decrease in overall cases was
244 considerably affected by the change in SFCT in VKHD cases. It is well known that the choroid
245 is the main site where disease-related ocular inflammation occurs in VKHD eyes, and thus
246 SFCT is used to monitor disease activity in VKHD [29,10,30,31,15,16]. Our results were
247 consistent with those in previous studies, in that the response to treatment was well
248 displayed on the choroidal OCT images in eyes with VKHD [29,10,30,15]. With regards to
249 non-VKHD, SFCT is unlikely to be a good biomarker, although its use might be beneficial in
250 some unclassified cases. Further studies are needed to elucidate whether SFCT monitoring
251 during adalimumab therapy is effective in each subgroup of uveitis.
252 Anatomically, the choroid consists of two major components, the choroidal vessels
253 and choroidal stroma, and OCT can depict these two components as luminal and stromal
254 areas, respectively. Agrawal R et al. utilised an OCT-based index, the choroidal vascular
255 index (CVI), defined as the proportion of the luminal area to the total choroidal area, for

monitoring disease activity in eyes with posterior or panuveitis [13]. Although CSI and CVI are similar measures (CSI = 1-CVI), we preferred to use CSI, because the choroidal stroma is the site of inflammatory cell infiltration. The ratio of the luminal area to the stromal area in our study seems to be consistent with that in the previous study, in that the mean CSI of 0.275 ± 0.050 at baseline in our study is well balanced with the mean CVI of the mean CVI of 0.741 ± 0.047 at baseline reported by Agrawal R et al [13]. The CVI data in our study are shown in Supplementary Figure 1. Unfortunately, our results suggest that the CSI is not a good marker to monitor the response to adalimumab therapy during the first 2 months. Kawano H et al. examined changes in CVI after the initiation of corticosteroid therapy in eyes with VKHD, and found that CVI was significantly increased from baseline to 1 week, but not from 1 week to 1 month [15]. Agrawal R et al. also observed CVI changes in VKH eyes treated with corticosteroid therapy, and showed that the CVI was significantly reduced from baseline to 6–12 months [32]. Therefore, further investigation is necessary to clarify which time point is most suitable for the evaluation of CSI as a marker of the response to adalimumab therapy.

The current study has several limitations, all of which are related to its retrospective nature and therefore should be resolved in a future prospective study. First, the sample size did not allow for a wide variety of causes of uveitis to be covered. Second, the data were incomplete regarding the factors that may affect the choroid (e.g., blood pressure, renal function and measurement time zone). Third, previous local corticosteroid therapy might affect the choroidal parameters following adalimumab b therapy. But we suppose the effect would be minimal because the last local corticosteroid (triamcinolone acetonide) injection was performed at least 2-3 months before the adalimumab initiation in most of the study eyes. Fourth, it remains unknown whether the short-term response observed in this study is related to the long-term response to adalimumab therapy, and the subsequent patient benefit.

In conclusion, this study supports the usefulness of OCT-based choroidal parameters as candidate biomarkers of the short-term response to adalimumab therapy. However, our results also indicate that further investigation is needed to exploit the potential of choroidal

283 imaging parameters. Novel insights extracted from extensive data in this field will help to
284 effectively treat refractory NIPPU with adalimumab and other biologics.
285

Compliance with Ethical Standards

Funding: No funding was received for this research.

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board (Kobe University Graduate School of Medicine) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Subject's informed consent was not required since this was a retrospective review.

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Figure Legends

Figure 1. Image processing to obtain a binary image of the choroid. (A) Select a 3,000 μm wide region of interest (ROI) centred on the fovea on each grayscale enhanced depth imaging optical coherence tomography (EDI-OCT) image. (B) Convert the image to a binary image. (C) Excise the binary image in the ROI and trace it by the Niblack method. (D) The traced binary image is superimposed on the original image.

Figure 2. Changes in the choroidal stromal index (CSI) and subfoveal choroidal thickness (SFCT) after adalimumab initiation. (A, B) Changes in the mean SFCT and CSI in all eyes (error bars represent standard deviation). (C, D) Changes in the mean SFCT and CSI in each disease group. VKHD: Vogt-Koyanagi-Harada disease, PAIR: Presumed autoimmune retinopathy.

Figure 3. Changes in choroidal imaging parameters following the initiation of adalimumab therapy in representative cases. SFCT: Subfoveal choroidal thickness, CSI: Choroidal stromal index.

437

438 Table 1. Patient Demographics at Baseline

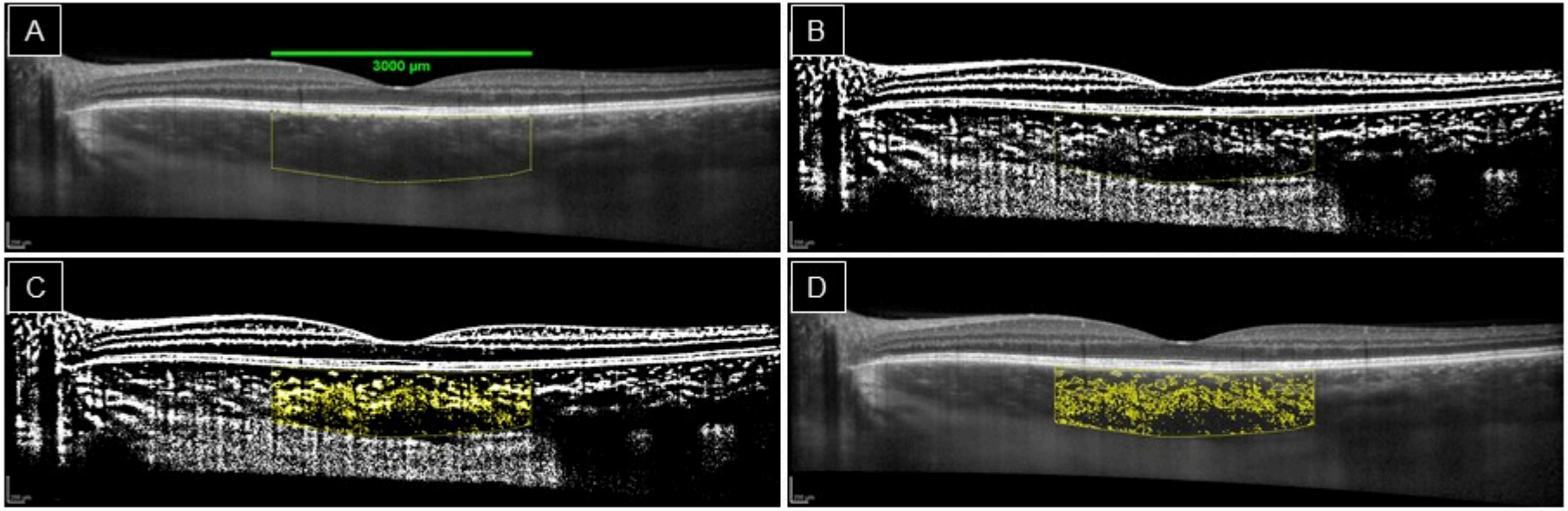
Demographic	Data
Number of patients/affected eyes, n/n	18/33
Age, mean (SD) years	58.4 (16.7)
Gender, men/women, n/n	6/12
Duration of uveitis, mean (SD) months	71.8 (75.2)
Anatomical type of uveitis, n (%)	
Intermediate uveitis	0 (0)
Posterior uveitis	14 (42.4)
Panuveitis	19 (57.6)
Pathological type of uveitis, n (%)	
Granulomatous	20 (60.6)
Non-granulomatous	6 (18.2)
Unknown	7 (21.2)
Cause of uveitis, n (%)	
Vogt-Koyanagi-Harada disease	14 (42.4)
Presumed autoimmune retinopathy	5 (15.2)
Sarcoidosis	2 (6.1)
Behçet's disease	2 (6.1)
Unclassified	10 (30.3)
Previous treatment*, n (%)	
Corticosteroids	22 (66.7)
Cyclosporine	15 (45.5)
Infliximab	2 (6.1)
Colchicine	2 (6.1)

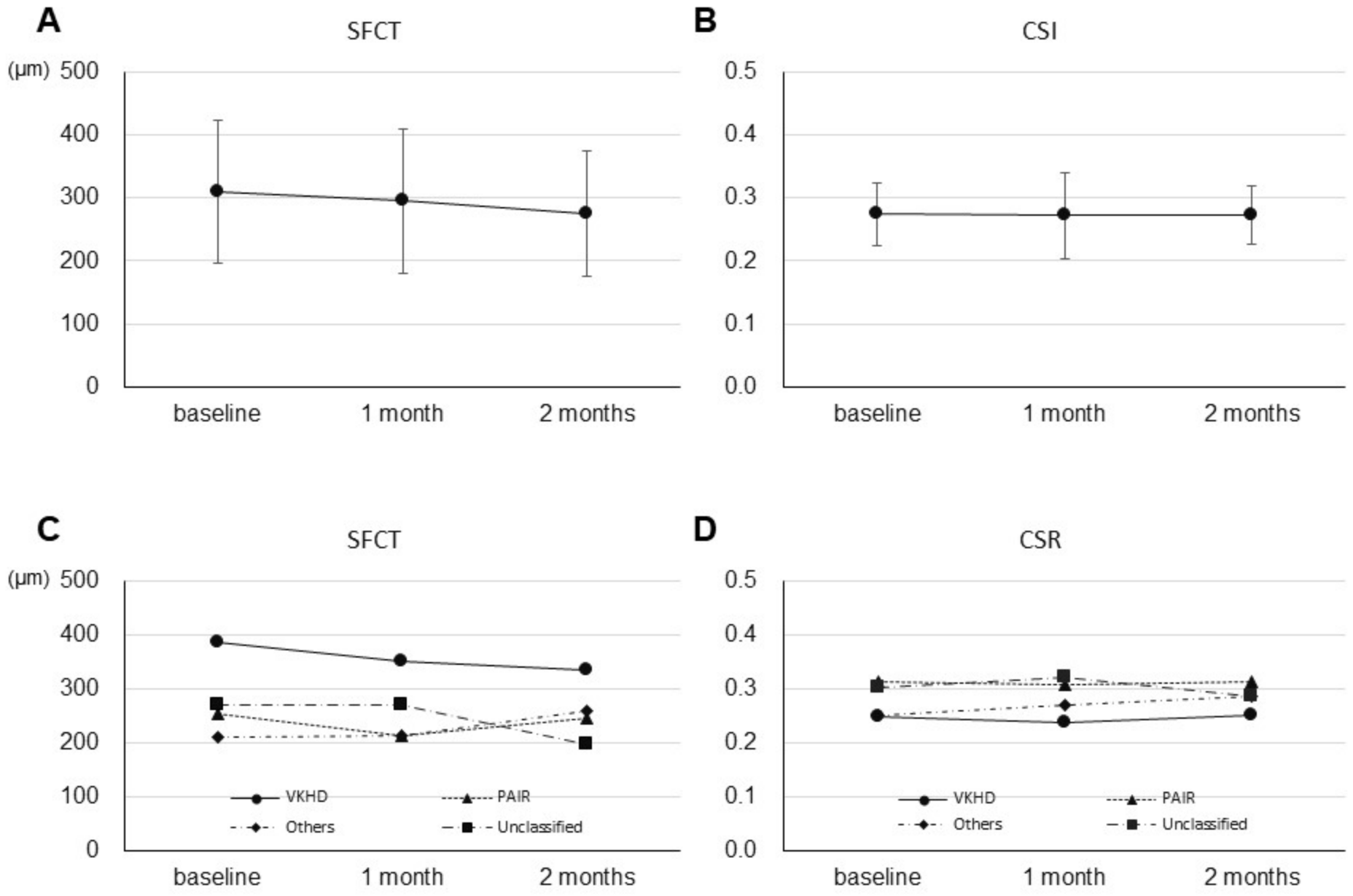
Sub-Tenon's triamcinolone acetonide	31 (93.9)
eGFR, mean (SD) (mL/min/1.73m2),	70.83 (17.14)

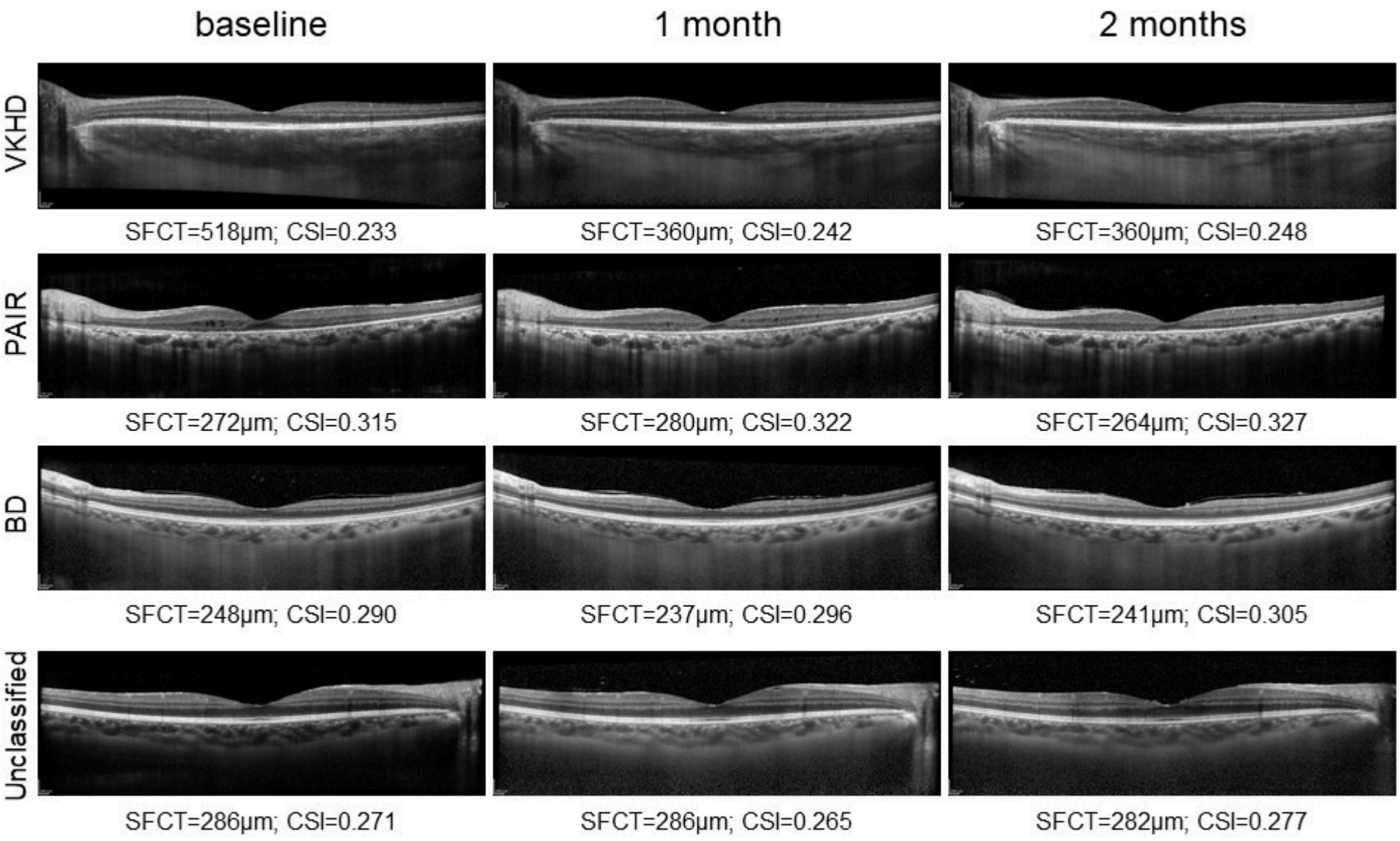
439 SD=standard deviation; eGFR= estimated glemerular filtration rate. *There is some

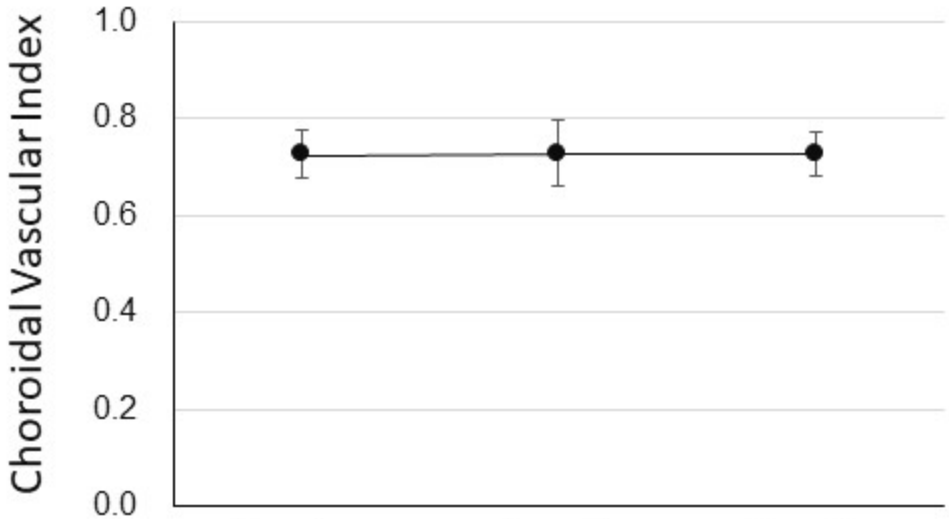
440 overlapping.

441


A
3000 µm
B
C
D


A
SFCT
(μm) 500
400
300
200
100
0
baseline
1 month
2 months
B
CSI
0.5
0.4
0.3
0.2
0.1
0.0
baseline
1 month
2 months
C
SFCT
(μm) 500
400
300
200
100
0
VKHD
PAIR
Others
Unclassified
baseline
1 month
2 months
D
CSR
0.5
0.4
0.3
0.2
0.1
0.0
VKHD
PAIR
Others
Unclassified
baseline
1 month
2 months


baseline
1 month
2 months
VKHD
SFCT=518μm; CSI=0.233
SFCT=360μm; CSI=0.242
SFCT=360μm; CSI=0.248
PAIR
SFCT=272μm; CSI=0.315
SFCT=280μm; CSI=0.322
SFCT=264μm; CSI=0.327
BD
SFCT=248μm; CSI=0.290
SFCT=237μm; CSI=0.296
SFCT=241μm; CSI=0.305
Unclassified
SFCT=286μm; CSI=0.271
SFCT=286μm; CSI=0.265
SFCT=282μm; CSI=0.277



	baseline	1 month	2 months
Mean	0.725	0.727	0.727
SD	0.050	0.068	0.046

Supplementary Figure 1. Changes in the choroidal vascular index following adalimumab initiation.
The mean choroidal vascular index showed no significant change between baseline and 2 months (P = 0.417). SD = standard deviation.