OCT Macular Volume as a Predictor of Vascular Leakage in Uveitis

Xiuju Chen · Wenyue Zhu · Xiaoxin Li

ABSTRACT

Introduction: This study aimed to evaluate the optical coherence tomography (OCT) macular volume as a marker for active vascular leakage in patients with intermediate and pan uveitis.

Methods: In this single-center prospective longitudinal study, patients were included under three criteria: diagnosed with noninfectious intermediate or pan uveitis; presented vascular leakage at their initial visit; and were imaged with concurrent wide-field fluorescein angiography (FA) and OCT. A scoring system was employed to measure vascular leakage. OCT volume scans were performed on the patients to produce the corresponding thickness map. The central subfield thickness (CST) and macular volume (MV) were calculated. CST is defined as the average thickness within the 1-mm fovea circle, while MV includes the 3-mm and 6-mm circles on the thickness map. Mixed-effects models were applied to analyze the correlation between each patient's OCT and FA imaging results.

Results: A total of 72 patients (115 eyes) were included. The median follow-up time was 11 months (interquartile range 1.8–16.1 months). A total of 679 observations across all time points were analyzed. Both CST and MV were found to be positively associated with the leakage scores ($p < 0.001$). In the mixed-effects models, MV in the 6-mm circle presented the strongest correlation with leakage scores, which explained 57% of the variation in leakage ($p < 0.001$). MV in the 3-mm circle and CST explained 45.8% and 39.5%, respectively.

Conclusion: CST and MV in both the 6-mm and the 3-mm circles demonstrated significant correlations with angiographic inflammatory activity. Among those imaging parameters, MV in the 6-mm circle has the highest correlation. The study results suggest that this parameter can be considered a quantitative and non-invasive alternative to FA for monitoring vasculitic inflammation in uveitis.

Keywords: Biomarkers; Fluorescein angiography; Uveitis; Optical coherence tomography; Vascular leakage

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Key Summary Points

The reliable assessment of intraocular inflammation in uveitis is essential in assessing the disease severity and response to treatment.

Retinal vascular leakage is an inflammatory sign in intermediate, posterior, and pan uveitis.

The severity of vascular leakage was highly correlated with optical coherence tomography measurements of macular volume.

Macular volume can be a non-invasive proxy of vascular leakage for monitoring the inflammatory activity in the treatment of patients with uveitis.

INTRODUCTION

Uveitis is a group of inflammatory disorders that accounts for 5–10% of worldwide visual impairment, largely affecting working-age individuals [1]. It is important to determine the degree of inflammation for appropriate treatment and to monitor the response to therapy [2–4]. Traditionally, the standardized method of grading uveitic disease activity is based on non-invasive clinical findings such as anterior chamber cell and flare, vitreous cells, and vitreous haze developed by the Standardization of Uveitis Nomenclature (SUN) working group [5]. However, the heterogeneity of vitreous haze and limited photographic views of the ocular fundus could hinder the precise assessment of ocular inflammation. Meanwhile, it is limited for assessment if the haze is mild, in particular, scoring 0.5 or 1 on the ordinal scale (4 being the maximum) [2, 6].

Other clinical signs of disease activity include decreased visual acuity, macular edema, and findings on fluorescein angiography (FA) such as vascular leakage and nonperfusion [7]. Visual acuity is not that sensitive to the improvement of inflammation. In the clinic, we routinely obtain ultra-widefield FA to assess vascular leakage in patients with uveitis, which primarily develops from the far periphery and then progresses to the mid periphery and macula with increasing vitreous cells. After treatment, the vascular leakage regressed to the far periphery. On the basis of our observation and previous studies, inadequate control of occult retinal vasculitis may lead to the inability to wean off immunomodulatory therapy, and long-term complications resulting in poor prognosis [8].

Though rare, FA could have potential side effects due to dye injection. The invasive nature of FA and the need for frequent monitoring of inflammation for proper management prompted us to find non-invasive alternative modalities of FA [9].

We have often observed concurrent retinal thickening in patients with a varying degree of FA leakage. A prior study reported retinal thickening in acute anterior uveitis without FA information [10]. Whether the retinal thickening is associated with the FA leakage and whether it changes in response to therapy are not comprehensively understood. On the basis of this background, we conducted a longitudinal study to evaluate the potential of the OCT metrics as a non-invasive alternative to FA for monitoring the inflammatory activity in uveitis.

METHODS

Patient Selection

This single-center prospective study was carried out in Xiamen Eye Center between March 2019 and July 2021. Patients are included under three criteria: diagnosed with noninfectious intermediate or pan uveitis; presented vascular leakage at their initial visit; and were imaged with concurrent wide-field fluorescein angiography (FA) and OCT. The diagnosis of intermediate uveitis and pan uveitis is based on the SUN working group.

The workup to determine etiologies of the uveitis was performed, including tuberculosis

skin test, serological tests for human immunodeficiency virus and syphilis, and radiological chest examination. Human leukocyte antigen B27, rheumatoid factor, anti-nucleotide antigen, and angiotensin-converting enzyme were determined in intermediate uveitis. Cerebral magnetic resonance imaging was performed in patients with neurologic symptoms.

The presence of significant media opacities (corneal band-keratopathy, cataract, and dense vitreous haze) that resulted in poor imaging quality preventing adequate assessment of angiographic leakage and the acquisition of OCT-derived macular metrics were excluded. Eyes with comorbidities such as diabetic maculopathy, high myopia, epi-retinal membrane formation, and macular atrophy associated with prolonged inflammation were also excluded, as were eyes with infectious uveitis and choroiditis. Furthermore, eyes that did not have either leakage scores or OCT measurements at baseline were excluded from the statistical analysis.

All subjects underwent a complete ophthalmic evaluation, including best corrected visual acuity (BCVA), slit-lamp examination, and dilated fundus examination for assessment of vitreous haze; and then ultra-widefiled FA and concurrent spectral-domain OCT imaging. BCVA was evaluated by Snellen electronic chart (NIDEK RT 5100) and then converted to logMAR (logarithmic minimum angle of resolution) for statistical analysis. Vitreous haze was categorized as absent (none/trace) or present ($\geq 1+$). Other variables collected include age, gender, systemic treatment, and local enhanced therapy.

Patients included had consented to take part in the study. Approval for data collection and analysis was obtained from the institutional review board of Xiamen Eye Center of Xiamen University (XMYK-KY-2019-005) and the study adhered to the tenets of the Declaration of Helsinki.

Acquisition and Grading of FA Images

All FA images were acquired using the Optos 200Tx UWF retinal imaging system (Optos PLC, Dunfermline, Scotland, UK). Vascular leakage was defined as increasing hyperfluorescence of retinal capillaries in the late-phase angiogram [11, 12]. One mid- to late-phase image (at 2–3 min) and a late-phase image (at 5–6 min) were chosen for grading retinal vascular leakage. Vascular leakage was localized by its distance from the macula (mid-periphery is anterior to arcades and posterior to the equator, far-periphery is anterior to the equator) (Fig. 1) and by quadrants centered on the macula such that eight zones were created [13]. Within each zone, a value of 0 was assigned if no leakage was identified, 0.5 if leakage was identified in less than half of the zone, and 1 if leakage occurred in greater than half of the zone. Vortex veins, the landmarks of the equator, are visible when setting the UWF color images on the red channel (635 mm) on the Optos Viewer [14]. FA image grading was performed by two masked physicians (XJC and XYY). If there was disagreement, a third senior physician (XXL) made the final judgement.

Acquisition and Analysis of OCT

OCT images were acquired by Spectralis HRA+ OCT (Heidelberg Engineering, Heidelberg, Germany). At each visit, a volume scan was performed that consisted of 19 horizontal B-scans within a fovea-centered area of 6.0×4.5 mm^2. OCT image analysis was performed using Heidelberg Eye Explorer Software (V.1.7.0.0., Heidelberg Engineering). Segmentation lines for the internal limiting membrane and Bruch's membrane were determined automatically on volume scan, and retina thickness maps were produced. An Early Treatment of Diabetic Retinopathy Study (ETDRS) grid was placed in the center of the fovea, which contains three rings with diameters of 1 mm, 3 mm, and 6 mm, respectively. The macula was divided into nine sectors according to the built-in grid. Automated measurements of the average thickness and the volume were recorded. Central subfield thickness (CST) was defined as the average thickness within the 1-mm fovea [15]. Macular volumes (MV) were defined as the sum of all zone volumes within the 6-mm circle and the 3-mm circle, respectively (Fig. 2).
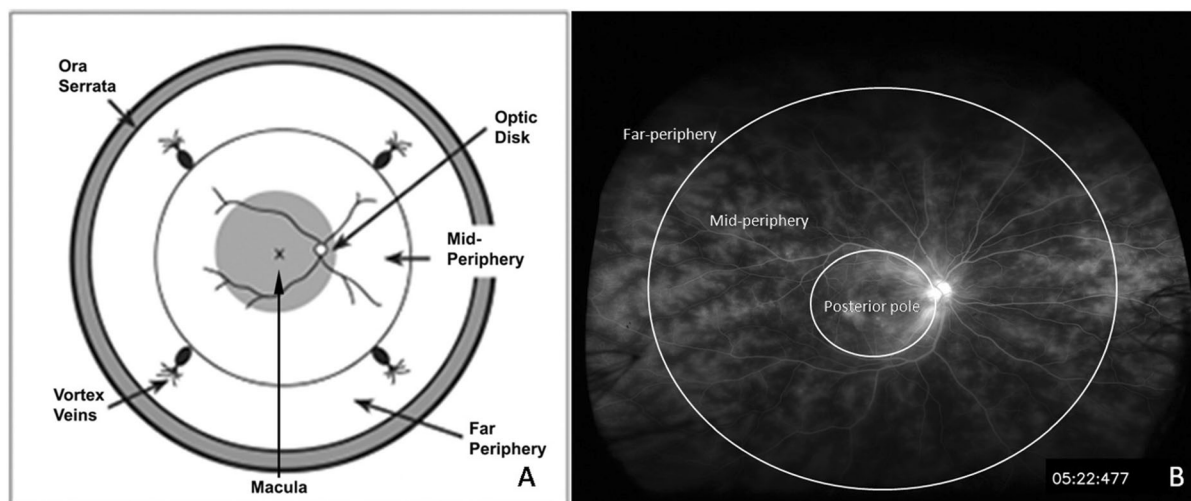
Fig. 1 **a** Illustration of the major landmarks of the retina and their positions. The circle crossing the vortex veins represents the equator. **b** Zones for determination of retinal vascular leakage (circles centered on the fovea): posterior—within the arcade; mid periphery—the zonal area outside the arcade and bordered by the equator; far periphery—area outside the equator

Statistical Analysis

We assessed the association between FA leakage scores and OCT measurements, including MV in the 3-mm circle, MV in the 6-mm circle, and CST using generalized linear mixed-effects (GLMM) models with the negative binomial link function. Random effects included a patient-specific effect to allow for the within-patient variation over time and a nested effect to adjust for the correlation between eyes from the same patient. Fixed effects included the time (in months), OCT metrics, the interaction term between OCT metrics and time, age, gender, BCVA, and whether the eye had treatment of local enhancement or not.

Comparisons were made among models that used different OCT metrics, via the assessment of model goodness-of-fit based on Akaike information criterion (AIC) values, deviance, and analysis of variance with OCT metrics as the independent variable.

In addition, we assessed the relationship between vitreous haze and FA leakage scores using a GLMM model with the binomial link. Vitreous haze (present vs none) is the dependent variable, and leakage score is the independent variable. Potential confounding factors include the time (in months), age, gender, VA and whether the eye had treatment of local enhancement or not. Adjustments of inter-eye correlation were made using nested random effects. The goodness-of-fit of the model was assessed using diagnostic plots.

The receiver operating characteristic (ROC) analysis was performed to examine whether vascular leakage was predictive of vitreous haze.

SPSS software was used to summarize baseline characteristics and to perform hypothesis testing. All regression models were fitted using R Statistical Software (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria). A p value less than 0.05 was considered to be statistically significant.

RESULTS

Demographic Characteristics and Clinical Features

A total of 115 eyes of 72 Asian patients were included in this study. The mean age at initial visits was 25.5 years (range 2–29, interquartile range 25). Out of 72 patients, 32 were female (44.4%), 30 (41.7%) had unilateral disease, and
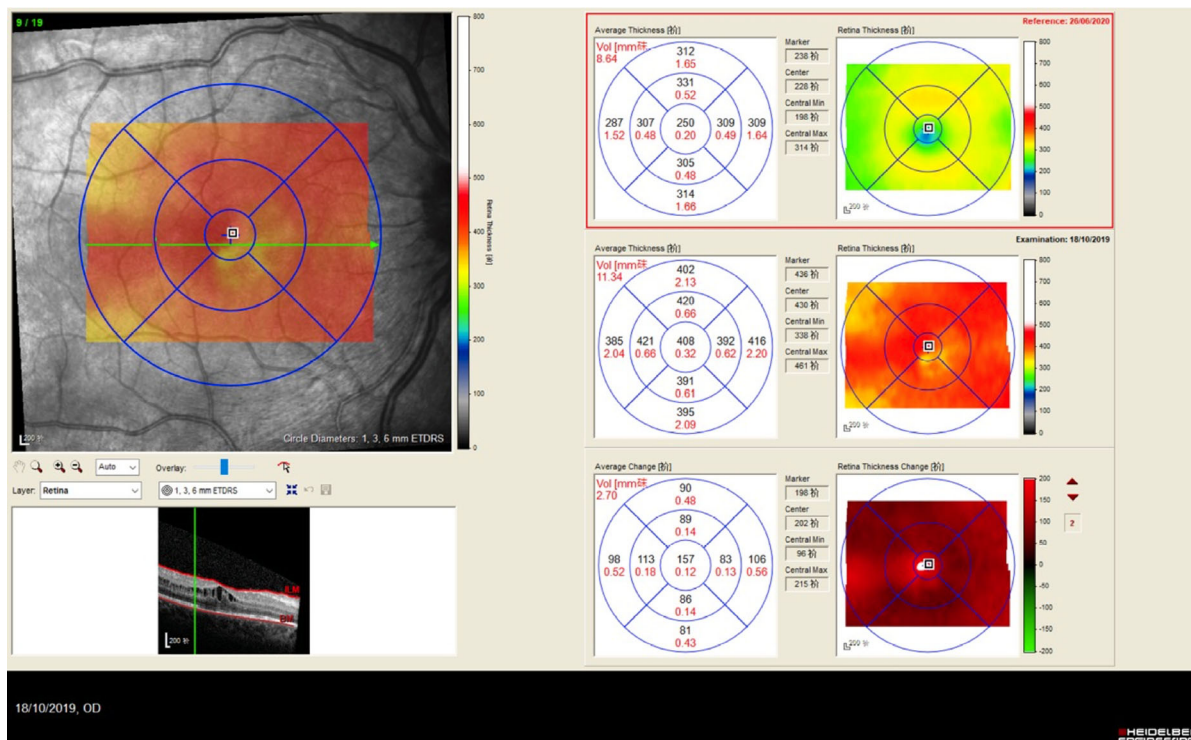
Fig. 2 Retinal thickness maps from the right eye of a 9-year-old female patient with macular edema taken with a Heidelberg Spectralis OCT system. Spectral-domain OCT showed an intra-retinal cyst. Heidelberg Eye Explorer software provides retinal thickness maps showing an even increase in retinal thickness due to the macular edema compared with the reference (upper right) with automated quantitative analysis of average change in different subfields of the macular grid. The reference scan shows the resolution of the "heat map" on the corresponding retinal thickness maps, together with automated quantitative analysis of average thickness (in black) and volume (in red) in different subfields of the macular grid

42 (58.3%) had bilateral involvement. Etiology of the uveitis included sarcoidosis in two patients (2.7%), HLA-B27-positive uveitis in six patients (8.3%), multiple sclerosis in four patients (5.6%), Behçet disease in six patients (8.3%), and the remaining subjects were considered as idiopathic (75.1%). All the eyes exhibited vascular leakage at baseline. Of the 72 patients, 45 (62.5%) subjects received systemic immunosuppressants. Demographic, baseline signs of inflammation, and disease characteristics are summarized in Table 1. At baseline, the vitreous haze was noted in 81 eyes (70.4%) and mean leakage scores were 5.3 (standard deviation, SD 3.2) with MV in the 6-mm circle 10.5 (1.4) mm^3, CST 343.6 (107.7) microns.

Longitudinal Observation of FA Leakage and OCT Metrics

Thirty-five patients (50 eyes) had been followed for more than 24 months. Out of 50 eyes, 32 exhibited diffuse vascular leakage, and 18 eyes showed leakage in the far-periphery at baseline. During the follow-up period, the leakage varied over time. Diffuse vascular leakage in the 32 eyes gradually regressed from mid-periphery to far periphery in response to oral corticosteroids with tapering or enhanced local treatment such as intravitreal/periocular steroids. In those eyes with decreasing extent of leakage, we observed spontaneously decreased OCT measurements (both CST and MV) (Fig. 3).

Additionally, eyes with more severe leakage (compared to eyes with less leakage) had

Table 1 Baseline demographic and clinical characteristics

Age (years), mean (SD)	25.5 (13.8)
Sex, n (%)	
Female	32 (44.4%)
Male	40 (55.6%)
Laterality, n (%)	
Unilateral	30 (40.3%)
Bilateral	42 (59.7%)
Baseline parameters	
Baseline BCVA (decimal Snellen), mean (SD)	0.6 (0.3)
Baseline CST (microns), mean (SD)	343.6 (107.7)
Baseline MV 6 mm, mean (SD)	10.5 (1.4)
Baseline VH present, n (%)	81 (70.4%)
Baseline leakage scores, mean (SD)	5.3 (3.2)
Baseline treatment, n (%)	
Disease-modifying antirheumatic drugs	45 (62.6%)
Associated systemic disease/etiology, n (%)	
Sarcoidosis	2 (2.7%)
Multiple sclerosis	4 (5.4%)
Behçet	6 (8.2%)
HLA-B27-related uveitis	6 (8.2%)
Idiopathic	55 (75.5%)
Follow-up (months), median (IQR)	11.2 (1.8–16.1)

SD standard deviation, *BCVA* best corrected visual acuity, *CST* central subfield thickness, *MV* macular volume, *VH* vitreous haze, *HLA-B27* human leukocyte antigen B27, *IQR* interquartile range

increased MV, even though no apparent retinal thickening was observed (Fig. 4).

Generally, there is a tendency for the extent of the vascular leakage to vary over time in concert with changes in the OCT measurements.

Association of FA Leakage Scores and Quantitative OCT Metrics

A total of 679 eye image sets (679 FA images, 679 OCT images) were analyzed from 72 patients (115 eyes) with a median follow-up of 11.2 months (interquartile range 1.8–16.1 months).

A scatterplot of FA leakage scores and MV was conducted and showed a positive relationship between leakage and MV. Such association ($p < 0.001$) was confirmed in the GLMM model with adjustment of inter-eye correlation and within-patient variation over time, adjusting for age, gender, and visual acuity. In the GLMM model, we included the interaction effect of macular volume and the time of measurement, which was also shown to be statistically
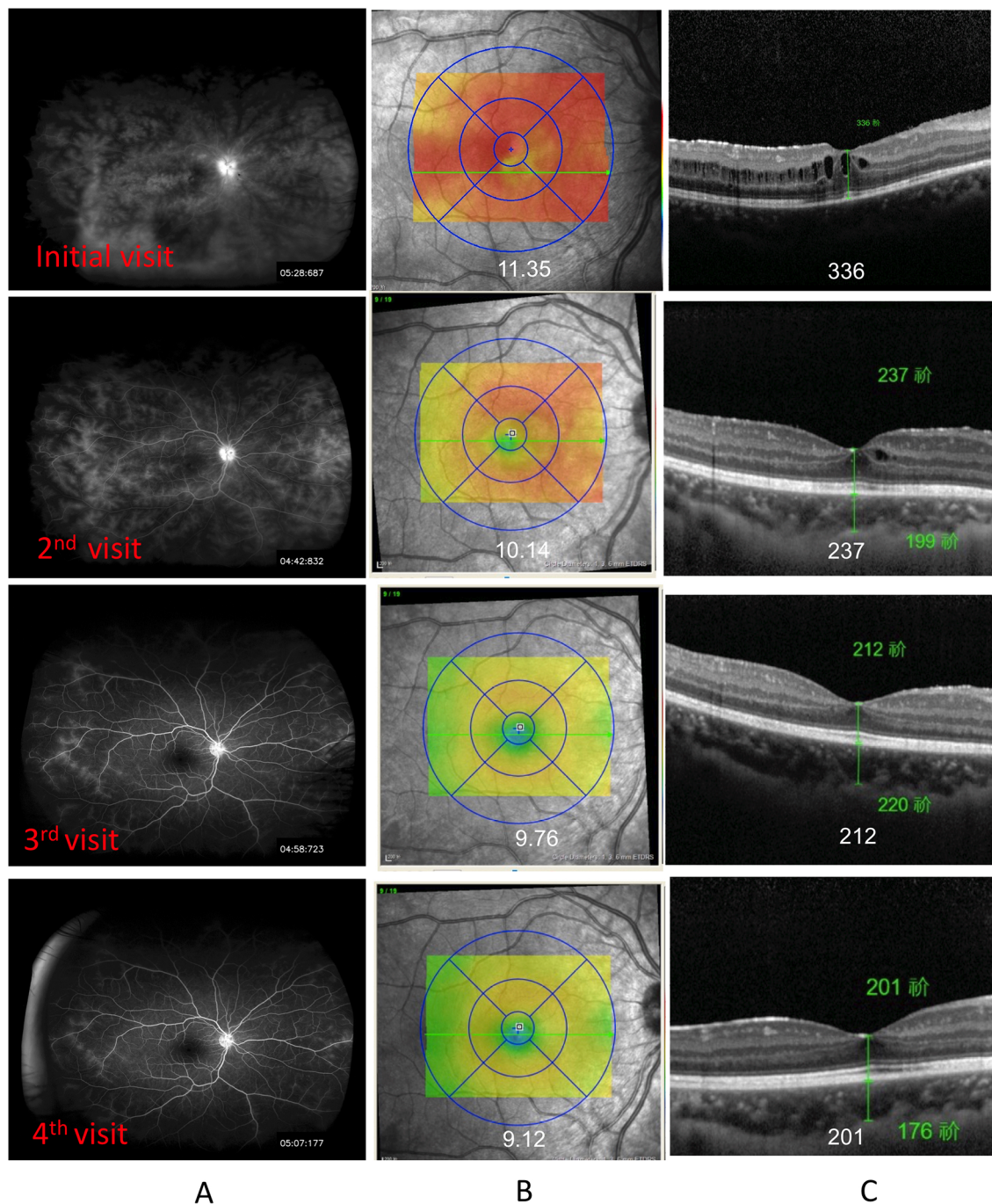
Fig. 3 A 9-year-old female patient presented with intermediate uveitis in her right eye. At the initial visit, the fluorescein angiographic image showed diffuse vascular leakage (**a**). At baseline, cystoid macular edema was noted on optical coherence tomography with a central subfield thickness (CST) of 336 μm (**c**) and macular volume (MV) in the 6mm circle of 11.35 mm^3 (**b**). She started on immunosuppression therapy, and on the follow-up visit, the leakage regressed to the far periphery (**a**), with a decreased CST of 328 μm (**c**) and MV of 10.14 mm^3 (the second visit, **b**). At the fourth visit, the leakage was only noted in the far periphery temporally (**a**). MV was decreased to 9.12 mm^3 (**b**) and CST to 250 μm (**c**)
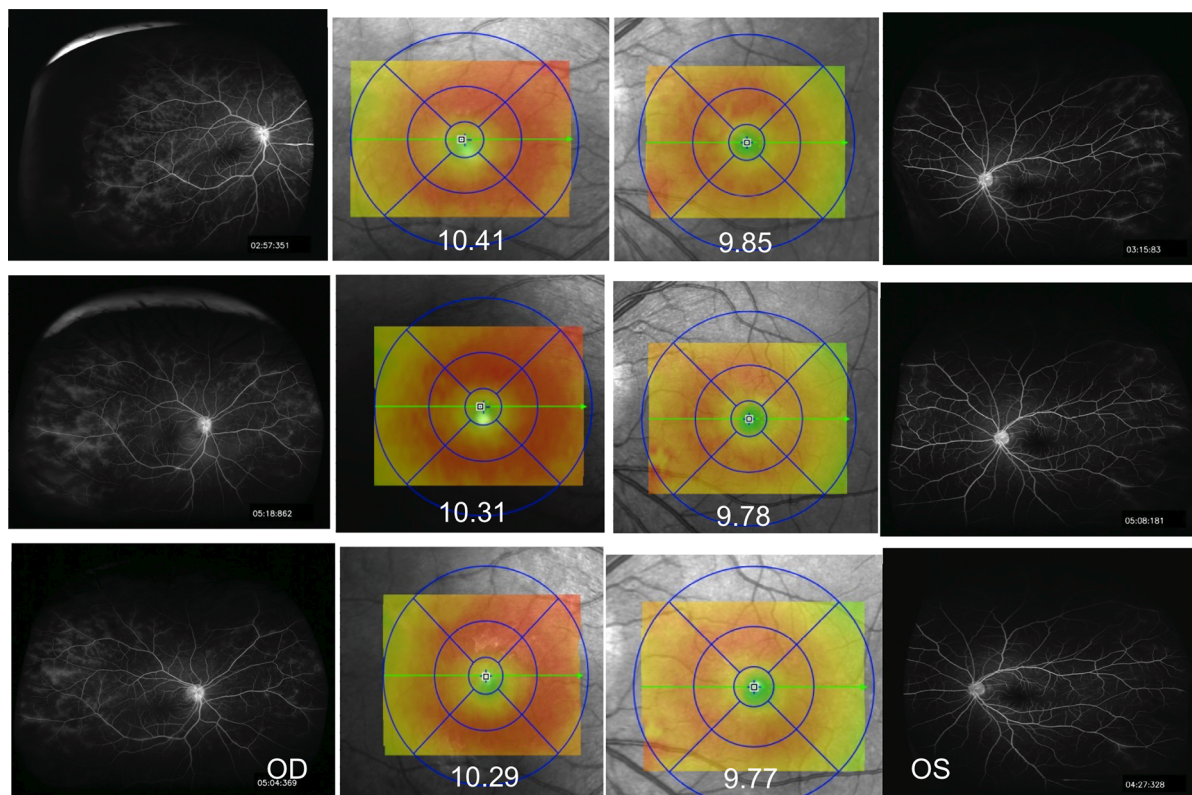
Fig. 4 Fluorescein angiographic images and corresponding OCT thickness maps over multiple visits in a 14-year-old female with bilateral intermediate uveitis. Vascular leakage was more severe in the right eye compared to the left during the follow-ups (the second and third columns). The corresponding retinal thickness map showed warm color in the right eye (OD) compared to that in the left eye (OS), even though there was no seemingly thickened macula in OCT images in both eyes

significant ($p < 0.001$). This indicates that the strength of the positive association between leakage scores and macular volume may change over time.

In addition, we used a GLMM model and found that CST was positively associated with the leakage scores ($p < 0.001$). In the model, we found that CST only explained 39.5% of the variation in leakage scores. By contrast, macular volume in 6-mm circle explained much larger variations, i.e., 56.2%, in leakage scores, and it gave a better model fit with smaller AIC and deviance values.

Noteworthy, macular volume in the 3-mm circle also demonstrated a positive association with the leakage ($p < 0.001$), and it explained 45.8% of the variation in leakage scores. It was shown in the analyses of variance that the GLMM model with macular volume in the 3-mm circle was better than the model with CST ($p < 0.001$), but less optimal in the model with macular volume in the 6-mm circle ($p < 0.001$). This indicates that macular volume in the 6-mm circle may be a better predictor of vascular leakage scores (see Supplementary Material).

Correlation of Clinical Findings with FA Leakages

We assessed the relationship between vitreous haze and FA leakage scores using a GLMM model with a binomial link. The leakage was found to be positively associated with the presence of vitreous haze ($p < 0.001$), accounting for inter-eye correlation and within-patient correlation over time. Eyes with one-unit increase in leakage score were more than two

AUC: 0.91 (95% Delong's CI: 0.88-0.93)
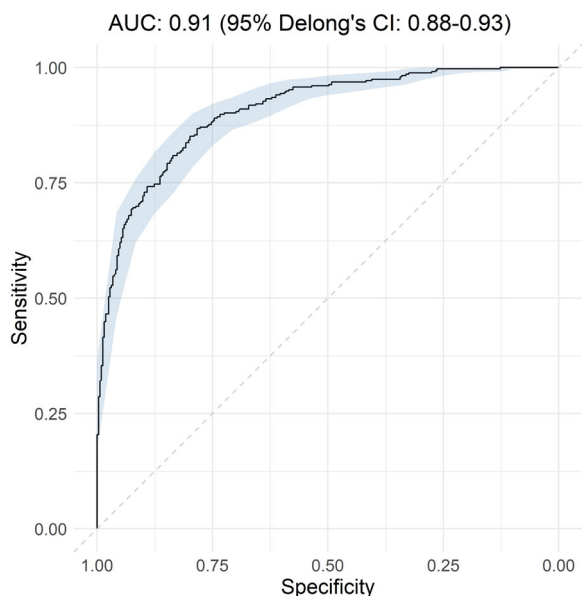
Fig. 5 Receiver operating characteristic (ROC) curve for the performance of leakage scores in distinguishing between eyes with vitreous haze present from those without. The area under the curve (AUC) and accompanying 95% confidence interval (CI) are shown

times as likely to have vitreous haze present, after adjusting for time of measurement, VA, age, gender, and whether it had local treatment or not (OR 2.69, $p < 0.001$).

Furthermore, ROC analysis was performed on the basis of the prediction outcome of vitreous haze using leakage scores from the GLMM model, which showed that the area under the ROC curve (AUC) is 0.91 (95% Delong's CI 0.88–0.93) (Fig. 5). This result revealed that leakage can be used as a predictor to distinguish eyes with vitreous haze present from those without.

Moreover, logMAR VA was found to be positively associated with vascular leakage scores ($p < 0.001$). Neither age ($p = 0.906$) nor gender ($p = 0.216$) was associated with the leakage scores.

DISCUSSION

Although clinical examination is commonly used for monitoring the severity of inflammation in patients with uveitis, it is not a sensitive parameter for treatment adjustment in patients with mild (none/trace) vitreous haze. FA

leakage, which is often present in intermediate uveitis and pan uveitis such as Behçet disease, was found to be correlated with macular edema and decreased on enhanced therapy [16–18]. At the uveitis endpoint workshop sponsored by the US Food and Drug Administration (FDA) and the National Eye Institute (NEI) held in 2015 in Holland, retinal vascular leakage was proposed to be regarded as a fundamental sign of inflammation in addition to anterior chamber cells and vitreous haze [3]. Our study demonstrated that FA leakage was a predictor or precursor of vitreous haze. In patients with uveitis and no or trace of vitreous haze, the inflammation of the vasculitis may be underestimated if not performing FA examination.

One of the major drawbacks of the FA is its invasive nature. As an alternative modality, OCT angiography (OCTA) has already produced a better understanding of retinal vascular disease in a non-invasive manner. However, OCTA is unable to detect leakage from retinal blood vessels and capillaries, which is the hallmark of vascular inflammation in uveitis and demonstrate the breakdown of inner blood-barrier.

In this cohort of patients with uveitis imaged with serial FA, we demonstrated that vascular leakage varied over time in concert with OCT metrics. MV increased during active vascular leakage and decreased with regression of leakage and can serve as a surrogate for FA leakage.

A significant finding in our study was that the MV in the 6-mm circle had a stronger association with vascular leakage (accounting for 57% of the variation), compared to MV in the 3-mm circle (45.8% of the variation) and CST (39.5% of the variation). Actually, CST was defined as average thickness within the 1-mm fovea of the macula. It is postulated that patients with active vascular leakage could have a diffuse spongy appearance of the retina, resulting in increased macular volume without noticeable changes in macular thickness. The minor changes in macular volume detected using tracked retinal thickness map analysis on OCT were mainly attributed to the retinal fluid alteration. Thus, retinal fluid changes on OCT may imply vascular leakage.

OCT MV is not an absolute proxy for FA, especially for the initial diagnosis of retinal

vascular leakage. In our clinic practice, OCT volume scans were performed on follow-up visits. In the cases of increased MV, FA can be obtained to confirm vascular leakage and evaluate the severity of leakage. On initial visits, the non-invasive OCT volume scans may detect increased vascular leakage and therefore the inflammatory activity, which may have otherwise gone unnoticed (e.g., in the absence of increased vitreous cell or haze or OCT findings). We found that the qualitative changes in color topography (yellow, orange, and red in the thickness map) are helpful and easy to obtain in clinical practice (Figs. 3, 4).

Compared with FA, the described method of using OCT volume scans to monitor vascular leakage has several limitations. Long-standing inflammatory macular thickening would result in macular atrophy or formation of epiretinal membrane, which were major confounding factors to MV. Epiretinal membrane is common in uveitis, with a prevalence of 48% [19, 20]. Thus, this method could not be generalized to subjects with a prolonged duration of uveitis. There is another limitation of this study. The scoring system of FA only reflects the area of leakage but does not consider the intensity of leakage. At the same time, it is subjective by graders, which may comprise the reliability of our study.

CONCLUSIONS

In summary, we conducted a longitudinal study on patients with intermediate and pan uveitis who were imaged with ultra-wide field FA and OCT. Our study suggests that OCT measurements, especially MV in the 6-mm circle, can be an alternative or implementation for quantitative measurement of active vascular leakage in patients with uveitis.

ACKNOWLEDGEMENTS

REFERENCES

1. Suttorp-Schulten MS, Rothova A. The possible impact of uveitis in blindness: a literature survey. Br J Ophthalmol. 1996;80(9):844–8. https://doi.org/10.1136/bjo.80.9.844.

2. Denniston AK, Keane PA, Srivastava SK. Biomarkers and surrogate endpoints in uveitis: the impact of quantitative imaging. Investig Ophthalmol Vis Sci. 2017;58(6):Bio131–40. https://doi.org/10.1167/iovs.17-21788.

3. Denniston AK, Holland GN, Kidess A, et al. Heterogeneity of primary outcome measures used in clinical trials of treatments for intermediate, posterior, and panuveitis. Orphanet J Rare Dis. 2015;10:97. https://doi.org/10.1186/s13023-015-0318-6.

4. Herbort CP Jr, Tugal-Tutkun I, Neri P, et al. Failure to integrate quantitative measurement methods of ocular inflammation hampers clinical practice and trials on new therapies for posterior uveitis. J Ocul Pharmacol Ther. 2017;33(4):263–77. https://doi.org/10.1089/jop.2016.0089.

5. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. Am J Ophthalmol. 2005;140(3):509–16. https://doi.org/10.1016/j.ajo.2005.03.057.

6. Keane PA, Karampelas M, Sim DA, et al. Objective measurement of vitreous inflammation using optical coherence tomography. Ophthalmology. 2014;121(9):1706–14. https://doi.org/10.1016/j.ophtha.2014.03.006.

7. Wintergerst MWM, Liu X, Terheyden JH, et al. Structural endpoints and outcome measures in uveitis. Ophthalmologica. 2021;244(5):465–79. https://doi.org/10.1159/000517521.

8. Abraham A, Saboo US, Ducca BL, et al. The detection of occult retinal vasculitis on fluorescein angiography in pediatric uveitis. Ophthalmol Retina. 2020;4(2):198–203. https://doi.org/10.1016/j.oret.2019.09.007.

9. Zarei M, Pesarakli H, Yaseri M, et al. Peripapillary optical coherence tomography as an alternative to fluorescein angiography for monitoring Behcet's retinal vasculitis. Sci Rep. 2021;11(1):20037. https://doi.org/10.1038/s41598-021-99485-5.

10. Traill A, Stawell R, Hall A, et al. Macular thickening in acute anterior uveitis. Ophthalmology. 2007;114(2):402. https://doi.org/10.1016/j.ophtha.2006.07.028.

11. Tugal-Tutkun I, Herbort CP, Khairallah M. Scoring of dual fluorescein and ICG inflammatory angiographic signs for the grading of posterior segment inflammation (dual fluorescein and ICG angiographic scoring system for uveitis). Int Ophthalmol. 2010;30(5):539–52. https://doi.org/10.1007/s10792-008-9263-x.

12. Antcliff RJ, Stanford MR, Chauhan DS, et al. Comparison between optical coherence tomography and fundus fluorescein angiography for the detection of cystoid macular edema in patients with uveitis. Ophthalmology. 2000;107(3):593–9. https://doi.org/10.1016/s0161-6420(99)00087-1.

13. Quinn N, Csincsik L, Flynn E, et al. The clinical relevance of visualising the peripheral retina. Prog Retin Eye Res. 2019;68:83–109. https://doi.org/10.1016/j.preteyeres.2018.10.001.

14. Laovirojjanakul W, Acharya N, Gonzales JA. Ultra-widefield fluorescein angiography in intermediate uveitis. Ocul Immunol Inflamm. 2019;27(3):356–61. https://doi.org/10.1080/09273948.2017.1371764.

15. Browning DJ, Glassman AR, Aiello LP, et al. Optical coherence tomography measurements and analysis methods in optical coherence tomography studies of diabetic macular edema. Ophthalmology. 2008;115(8):1366-71.e1. https://doi.org/10.1016/j.ophtha.2007.12.004.

16. Thomas AS, Redd T, Campbell JP, et al. The impact and implication of peripheral vascular leakage on ultra-widefield fluorescein angiography in uveitis. Ocul Immunol Inflamm. 2019;27(3):349–55. https://doi.org/10.1080/09273948.2017.1367406.

17. Keino H, Okada AA, Watanabe T, et al. Long-term efficacy of infliximab on background vascular leakage in patients with Behçet's disease. Eye (Lond). 2014;28(9):1100–6. https://doi.org/10.1038/eye.2014.138.

18. Keino H, Okada AA, Watanabe T, et al. Decreased ocular inflammatory attacks and background retinal and disc vascular leakage in patients with Behcet's disease on infliximab therapy. Br J Ophthalmol. 2011;95(9):1245–50. https://doi.org/10.1136/bjo.2010.194464.

19. Nicholson BP, Zhou M, Rostamizadeh M, et al. Epidemiology of epiretinal membrane in a large cohort of patients with uveitis. Ophthalmology. 2014;121(12):2393–8. https://doi.org/10.1016/j.ophtha.2014.06.015.

20. Kempen JH, Altaweel MM, Holbrook JT, et al. The multicenter uveitis steroid treatment trial: rationale, design, and baseline characteristics. Am J Ophthalmol. 2010;149(4):550-61.e10. https://doi.org/10.1016/j.ajo.2009.11.019.