Analysis of choriocapillaris perfusion and choroidal layer changes in patients with chronic central serous chorioretinopathy randomised to micropulse laser or photodynamic therapy

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ABSTRACT

Purpose The purpose of this study was to investigate the signal changes in choriocapillaris flow deficits and choroidal thickness changes using swept-source optical coherence tomography angiography (OCTA) following different treatments.
Design A double-blind, randomised controlled trial.
Methods Patients with unilateral chronic central serous chorioretinopathy (CSC) were randomised to receive subthreshold micropulse laser therapy (MLT) or half-dose photodynamic therapy (PDT). Choroidal thickness and choriocapillaris flow deficit signals were investigated.
Results Eighteen patients were randomised into the MLT group and 15 patients into the PDT group. Areas with flow deficit signals were identified in all baseline OCTA images of the choriocapillaris, with mean areas of 0.420 and 0.465 mm^2 in the MLT and PDT groups, respectively. These flow deficit signal areas were significantly reduced at 6 months (p=0.011) in the MLT group and at 3 months (p=0.008) in the PDT group. Patients from the PDT group were shown to have smaller flow deficit areas than patients from the MLT group at all time points after treatment (p=0.001, analyses of variance). The mean choroidal volume of the fovea showed a significant reduction at 1 month (p=0.003), 3 months (p=0.199) and 6 months (p=0.006) in the PDT group.
Conclusion The flow deficit areas identified in the choriocapillaris layer may suggest possible relative choroidal ischaemia. With measurement of choroidal volume reduction and faster rates of flow deficit area change, PDT has a stronger effect than MLT in promoting choriocapillaris recovery.

INTRODUCTION

Central serous chorioretinopathy (CSC) is a disease with serous macular detachment due to various aetiologies. This disease falls into the spectrum of pachychoroid disease.[1 2] The dilated choroidal vessels at the outer choroidal layer, known as pachyvessels, are suggested to have a mechanical compression effect on the retinal pigment epithelium (RPE)–Bruch's membrane layer and the choriocapillaris layer, leading to choriocapillaris hypoperfusion and RPE barrier breakdown.[3] Treatments are generally required in chronic CSC (cCSC) cases, as persistent subretinal fluid (SRF) can cause irreversible damage to the photoreceptors leading to visual loss.[4]

Various treatment methods have been previously reported for cCSC. Given the lack of prospective studies available, there is no consensus on the optimal treatment for cCSC. Two laser treatment modalities are widely adopted for treatment of cCSC, namely the half-dose photodynamic therapy (PDT) and micropulse laser therapy (MLT). MLT works by delivery of brief subthreshold micropulse laser to the RPE, raising the temperature of the RPE without exceeding the protein denaturing threshold. This leads to activation of the RPE cells and increased fluid absorption.[5 6] PDT, on the other hand, is believed to act directly on the choroid causing transient choroidal ischaemia and subsequent choroidal vascular remodelling.[7] Both treatments have reported success rates of 41–100% in treatment of cCSC. Recently, the PLACE trial, a multicentred randomised control trial, demonstrated half-dose PDT being superior to subthreshold macular laser in terms of anatomic and functional outcomes.[8] However, there is currently no consensus on which treatment should be adopted as the gold standard. Our work aims to study the choroidal changes on optical coherence tomography angiography (OCTA) following different laser therapies.

OCTA was adopted in the evaluation of retinal and choroidal vasculature without using dye. Several studies recently reported the choriocapillaris characteristics in eyes with CSC using OCTA analysis.[9–12] Irregular choriocapillaris flow patterns or flow deficit patterns were observed in eyes with CSC,[12 13] which may suggest choriocapillaris ischaemia. PDT was shown to promote choriocapillaris flow deficit recovery in CSC cases.[14 15] However, there is still a lack of understanding on the respective mechanisms of PDT and micropulse laser therapy (MLT) in the treatment of CSC.

Considering the nature of pachychoroid diseases, we investigated the choroidal parameters of eyes with CSC in the hope to better understand the pathophysiology of CSC and the mechanisms of current treatments. Thus, OCTA and en-face optical coherence tomography (OCT) were adopted to capture the features of choriocapillaris blood flow and choroidal volume. Changes in the choroidal features were evaluated for both groups after receiving either MLT or PDT.

METHODS

Study design

Consecutive patients with a history of CSC longer than 3 months were recruited between January 2016 and June 2018. The exclusion criteria included a history of prior macular laser or PDT, use of systemic steroids, multifocal CSC and evidence of diffuse retinal pigment epitheliopathy. Patients with fibrin, pigment or pigment epithelial detachment in the macula, which may produce shadow artefacts in OCTA, were also excluded. The recruited patients were randomised into two treatment groups: group 1—subthreshold MLT and group 2—half-dose PDT. Block randomisation was performed, and a computer-generated randomisation number in a block size of 4 was created by an independent research assistant who also carried out the treatment allocation process.

All patients were assessed at baseline, 1 month, 3 months and 6 months after the treatment. The patients underwent treatment every 3 months if they showed persistent fluid on OCT (Triton DRI-OCT; Topcon, Tokyo, Japan). At each visit, the patients underwent detailed clinical examination, including visual acuity (VA), dilated funduscopy, fluorescein angiography, indocyanine green angiography (ICGA), autofluorescence scans using Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), OCT structural scans and OCTA scans (Triton DRI-OCT) using the same setting.

Laser treatments

A grid pattern of micropulse yellow (577 nm; MicroPulse TxCell Scanning Laser Delivery System; Iridex, Mountain View, California, USA) was applied over the area of SRF using a spot size of 200 µm, power of 340–400 MW and duration of 200 ms with 5% duty cycle. In those cases, where the site of leakage on fluorescein angiogram was extrafoveal, a focal laser was applied to the area of leakage using a spot size of 100 µm, power of 80–150 MW and duration of 15 ms.

The PDT was performed using half-dose (3 mg/m^2) verteporfin (Visudyne; Novartis, Basel, Switzerland), which was infused over 10 min. Five minutes later, laser therapy was applied for 83 s.[16] Full-fluence PDT (50 J/cm^2) was applied to the area of choroidal hyperpermeability on ICGA with a margin of 500 µm.[17]

In this double-blind study, the patients who were randomised to MLT received a sham intravenous injection of normal saline and sham PDT, while patients in the PDT group received sham MLT. A separate group of retinal specialists applied the therapies and the principal investigators were masked to the patients' treatment allocation.

OCTA image acquisition and analysis

All patients underwent OCTA with a swept-source OCT (Triton DRI-OCT), which has a light source with a 1050 nm wavelength and a speed of 100 000 A-scans per second. The swept-source OCT was performed by trained examiners after pupil dilation. Volumetric OCT scans centred on the fovea were obtained with a scan area of 3 mm × 3 mm containing 320×320 A-scans. Topcon's built-in software (ImageNet 6) was used to generate OCT-A images with improved detection sensitivity of low blood flow and reduced motion artefacts. The software automatically detected four horizontal depth-resolved slabs on OCT-A images, and the optical slab for the choriocapillaris was used for the analysis. It was automatically set at 10.4 µm below the basement membrane. Images that contained segmentation algorithm failures, motion artefacts or poor focus were excluded from the analysis.

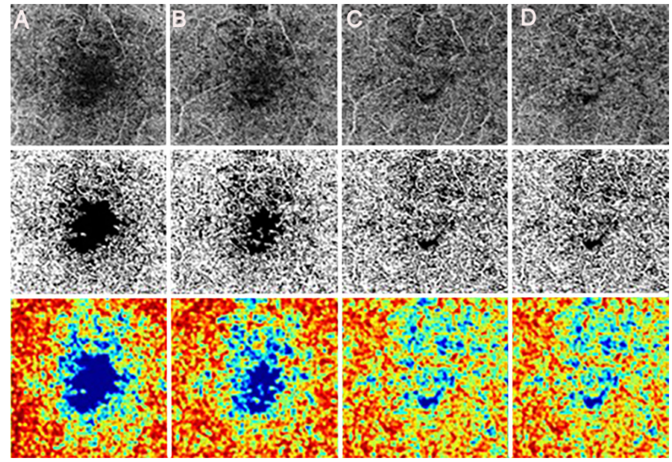

Figure 1 Optical coherence tomography images of choriocapillaris (top row), binarised images (second row) and images showing the vascular density colour-coded picture (third row) using a custom-made MATLAB program. These pictures were obtained from a patient with good past health, whose left eye suffered from chronic central serous chorioretinopathy, and who received micropulselaser therapy in our study. From the top right to the top left, these pictures represent different time points at baseline (A), 1 month (B), 3 months (C) and 6 months (D). The vascular density images in the bottom row were imported to ImageJ, where the regions of interest were mapped out with densities <20% (colour-coded blue) which are defined as flow void areas in our study. The total colour-coded blue area is represented in mm^2.

The en-face images of the OCT angiograms were exported in greyscale using ImageNet 6. The images were then imported into an automated customised MATLAB program (MathWorks, Natick, Massachusetts, USA) for image analysis. A custom semiautomated algorithm was developed[18] and used to quantify several parameters that describe vascular density (VD) and morphology.[19] To quantify these parameters, the greyscale two-dimensional en-face OCTA image was first converted into an 8-bit image (586×585 pixels), encompassing a 3×3 mm area around the fovea (1 pixel ≈ 5.13×5.13 µm^2, figure 1, first row). This image was converted into a binary image (figure 1, second row) using a three-way combined method consisting of a global threshold, hessian filter and adaptive threshold in MATLAB (R2013b; MathWorks).[20] The flow deficit areas were defined as a VD of <20% and mapped as colour-coded blue (figure 1, third row). The images colour-coded for VD were then imported into ImageJ software (V.1.46) where the flow deficit areas of the choriocapillaris were marked automatically with the region of interest (ROI) defined as areas with VD <20%. The pixel numbers of ROI were converted into an area measurement in mm^2.

Outcomes and statistical methods

The primary outcomes focused on the changes in the choriocapillaris layer perfusion captured by OCTA. The continuous variables were compared using a two-tailed t-test for parametric distribution. The analysis of variance (ANOVA) test was adopted for variables using repeated measures. The statistical analysis was performed using SPSS software (V.20.0; IBM SPSS). Binary logistic regressions were performed for the dependent outcomes

Table 1 Demographic and clinical information of CSC patients in the two groups of laser treatments

	Micropulse group		Half-dose PDT group	P value
Age (years)	53.17±10.48		50.93±11.01	0.480
Sex (male:female)	14:4		11:4	0.418 (χ^2)
Right eye:left eye	12:6		6:9	
Axial length (mm)	23.49±1.05		23.20±0.64	0.351
Spherical equivalent (D)	−0.15±2.24		0.17±0.85	0.605
Symptoms duration (months)	8±4.3		5.8±1.21	0.334
CMT at baseline (µm)	396.50±116.86		368.00±86.70	0.440
CMT at 1 month (µm)	312.67±80.96	0.001* (p value compared with baseline)	219.87±45.53	<0.001* (p value compared with baseline)
CMT at 3 months (µm)	277.61±89.53	<0.001* (p value compared with baseline)	228.53±42.75	<0.001* (p value compared with baseline)
CMT at 6 months (µm)	234.06±32.81	<0.001* (p value compared with baseline)	221.60±73.76	<0.001* (p value compared with baseline)
VA at baseline (logMAR)	0.31±0.30		0.23±0.20	0.955
VA at 1 month (logMAR)	0.22±0.16	0.126 (p value compared with baseline)	0.12±0.07	0.049* (p value compared with baseline)
VA at 3 months (logMAR)	0.16±0.13	0.062 (p value compared with baseline)	0.10±0.09	0.036* (p value compared with baseline)
VA at 6 months (logMAR)	0.11±0.06	0.005* (p value compared with baseline)	0.09±0.06	0.014* (p value compared with baseline)
Proportion achieved dry fovea at 3 months	9 (9/18)		13 (13/15)	0.030* (Fisher's exact test)

*Statistically significant.
CMT, central macular thickness; CSC, central serous chorioretinopathy; PDT, photodynamic therapy; VA, visual acuity.

of successful treatment, which were determined as yes/no dry fovea. A p value of <0.05 was considered statistically significant.

RESULTS

Demographic data

Thirty-three patients were enrolled in this study: 18 patients received subthreshold MLT and 15 patients received half-dose PDT. The male-to-female ratio was 25:8. The mean age of recruited patients was 52.15±10.61 years. The mean symptoms duration was 6.7±2.9 months (range 4–13 months). Table 1 summarises the demographic and clinical information for the recruited patients.

Treatment response

The baseline VA was 0.18±0.14 logMAR in the MLT group and 0.23±0.27 logMAR in the PDT group. The VA in the PDT group was significantly improved to 0.20 logMAR at 3 months (p=0.027), while the VA in the MLT group was significantly improved to 0.16 logMAR at 6 months (p=0.012). The baseline central macular thickness was 414.1±27 µm in the MLT group and 357.1±21 µm in the PDT group. Both groups showed significant improvement in the central macular thickness at 1 month: that is, 319.56 µm (p=0.001) in the MLT group and 232.64 µm (p=0.018) in the PDT group.

At 3 months, 9 cases (9/18) in the MLT group achieved complete SRF resolution, while 13 cases (13/15) in the PDT group achieved complete SRF resolution. More patients in the PDT group achieved successful treatment outcomes with complete SRF resolution at 3 months (p=0.030, Fisher's exact test; table 1).

Choriocapillaris layer features

Quantitative OCTA parameters for flow signal deficits in the patients with CSC are shown in table 2. The mean total area of flow deficit signals at baseline was similar between the two groups (0.319±0.301 mm^2 in the MLT group vs 0.231±0.203 mm^2 in the PDT group). Both groups showed reduction in the total area of flow deficit signals at subsequent follow-up visits compared with baseline. Significant reductions in the quantitative flow deficit areas were observed early in the PDT group at 1 month (0.120±0.069 mm^2; p=0.049). This reduction in the flow deficit size was observed at 6 months in the MLT group (0.111±0.061 mm^2; p=0.005) (table 2).

The ANOVA test was adopted to detect any difference in the flow deficit areas of the two groups after receiving treatment. The flow deficit areas at 1, 3 and 6 months were included for analysis. Patients receiving half-dose PDT showed a significantly smaller flow deficit area than patients in the MLT group at all time points after receiving treatment (F=9.982, p=0.001, Greenhouse–Geisser test).

Choroidal volume change after laser therapy

Table 3 summarises the mean choroidal volume in each area of the EDTRS map in the two groups. The mean choroidal volume

Table 2 Optical coherence tomography angiography quantitative parameters of flow signal voids in affected eye of the two groups

	MLT group			PDT group	
Baseline Mean of flow void area±SD (mm^2)	0.319±0.301			0.231±0.203	P=0.350†
1 month Mean of flow void area±SD (mm^2)	0.227±0.166	P=0.126		0.120±0.069	P=0.049*
3 months Mean of flow void area±SD (mm^2)	0.164±0.131	P=0.062		0.101±0.090	P=0.036*
6 months Mean of flow void area±SD (mm^2)	0.111±0.061	P=0.005*		0.098±0.057	P=0.014*
ANOVA test	Sphericity test p value <0.01		F value (1.394, 43.212) =9.982	Greenhouse–Geisser p value 0.001*	

*Statistically significant.
†P value compared between PDT and MLT groups.
ANOVA, analysis of variance; MLT, micropulse laser treatment; P, P value compared with baseline; PDT, photodynamic therapy.

Table 3 Choroidal volume measurement for early treatment diabetic retinopathy study rings in MLT and PDT groups, respectively, at different time points

	Centre±SD (mm^3)				Inner ring±SD (mm^3)				Total EDTRS±SD (mm^3)			
	MLT		PDT		MLT		PDT		MLT		PDT	
	Centre±SD (mm^3)	P	Centre±SD (mm^3)	P	Inner ring±SD (mm^3)	P	Inner ring±SD (mm^3)	P	Total EDTRS±SD (mm^3)	P	Total EDTRS±SD (mm^3)	P
Baseline	298±67		340±84	0.208†	1458±307		1205±690	0.223*	2525±518		2074±1200	0.286†
1-month post-treatment	305±63	0.316	280±94	0.003*	1499±281	0.321	1351±498	0.378	2398±795	0.601	1867±1255	0.379
3-month post-treatment	312±74	0.199	278±72	0.007*	1509±339	0.271	1328±430	0.252	2620±555	0.208	2355±790	0.352
6-month post-treatment	323±72	0.066	293±75	0.006*	1598±327	0.052	1540±439	0.795	2762±571	0.053	2709±903	0.703

*Statistically significant.
†P value compared between PDT and MLT groups.
MLT, micropulse laser treatment; P, P value compared with baseline; PDT, photodynamic therapy.

of the fovea at baseline was 298±67 mm^3 in the MLT group and 305±63 mm^3 in the PDT group.

Among the different choroidal volume measurements, the foveal choroidal volume for the PDT group showed significant reductions at 1 month (p=0.003), 3 months (p=0.007) and 6 months (p=0.006). In contrast, the foveal choroidal volume of the MLT group was static over time (table 3). The mean choroidal volume of the inner ring and total EDTRS (Early Treatment Diabetic Retinopathy Study) map did not show any significant change over time in the two groups. Figure 2A–C shows the changes on the colour-coded choroidal thickness map and the mean choroidal volume of a patient who received PDT treatment.

Predictors of foveal SRF status

We conducted a logistic regression that included all cases for analysis. The baseline foveal choroidal volume, the baseline flow deficit areas and the treatment modalities served as predictor variables, while the outcomes for macular dryness at 6 months were considered as outcome variables. In the binary logistic regression, we found that smaller flow deficit areas at baseline (p=0.038, coefficient: 0.130) and using PDT treatment (p=0.034, coefficient: −1.055) predicted favourable outcome at 6 months. In contrast, the foveal choroidal volume was not found to be associated with the treatment outcome at 6 months (p=0.554, coefficient: −0.001). Details of the analysis were listed in online supplementary table 1.

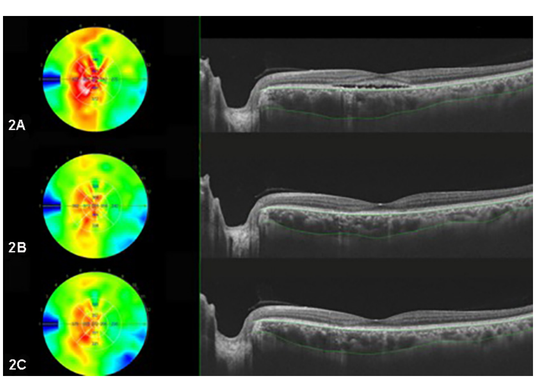

Figure 2 Changes in the colour-coded choroidal thickness map and mean choroidal volume of each subfield of the early treatment diabetic retinopathy study grid. (A–C) Colour-coded choroidal map and choroidal volume measurements of the left eye of a patient receiving PDT. The patient's baseline foveal choroidal volume was 427 mm^3, which was gradually reduced to 381 and 372 mm^3 at subsequent visits. The colour-coded map shows a prominent reduction in choroidal thickness at 1 month (B) and 3 months (C) after PDT. PDT, photodynamictherapy.

DISCUSSION

This study obtained several key findings. First, flow deficit areas with suspected choriocapillaris hypoperfusion were identified in all CSC cases at baseline. Second, gradual reduction of flow deficit areas was observed in both treatment groups. Using a repeated-measure ANOVA test, the PDT group was found to have more prominent flow deficit area reduction compared with the MLT group.

Recently, more OCTA analyses have provided evidence suggesting choroidopathy and altered choroidal vascular pattern in CSC cases. Teussink *et al* reported irregular flow patterns with areas of hyperperfusion and foci of impaired flow.[13] Rochepeau *et al* reported quantifiable flow deficit areas, suggesting choriocapillaris hypoperfusion and microvascular deficits in diseased eyes.[21] Similarly, Yun *et al* reported similar hypoperfusion areas in the fellow eyes of acute CSC cases.[3] In addition, Costanzo *et al* showed dark spots or dark areas within the choriocapillaris in CSC eyes using OCTA imaging.[22] Considering treatment benefits, PDT was shown to promote choriocapillaris flow recovery in persistent CSC, although the presence of subretinal detachment may affect the reliability of flow signal interpretation.[15] Fujita *et al* investigated the effect of PDT on choroidal vasculature using OCTA analysis. Similar to our findings, the flow deficit at baseline decreased significantly at 1 month after half-dose PDT.[23] Nassisi *et al* observed a change in the choriocapillaris vessels density after PDT, with initial reduction in vessel density and gradual improvement at 1 month.[24] In concordance with the above studies, our study showed that PDT have predominant effect in promoting choriocapillaris flow recovery in persistent CSC.

In pachychoroid eyes, the abnormally dilated choroidal vessels cause direct compression of the overlying choriocapillaris, which may have limited elasticity or compliance for adjustment in CSC eyes.[2 25] This hypothesis was further supported by choroidal imaging using enhanced depth imaging, showing thinning of the inner choroid and enlarged outer choroidal lumina.[26] Blood flow may be limited in the compressed choriocapillaris, which causes focal ischaemia. Hence, the barrier function of the choriocapillaris–RPE complex can be altered, leading to fluid accumulation in CSC cases. Our study provides supporting evidence for this hypothesis.

Spaide suggested a protocol to analyse the flow deficit areas in greyscale OCTA images of choriocapillaris and reported measurable changes in the OCTA patterns of choriocapillaris associated with age, hypertension, pseudodrusen and age-related macular degeneration,[27] as well as in other retinal diseases.[28] The current study adopted a variant of the analysis method based on Spaide's protocol by adopting MATLAB to calculate the VD. This method may increase the sensitivity of identifying limited flow signal areas, as a VD of <20% was considered as a flow deficit area in this study. However, the authors have chosen an arbitrary cut-off of <20% vessels density to identify the flow deficit areas. In a setting of OCTA analysis of the retinal capillary plexus, avascular areas are well-validated with the foveal avascular zone set as reference level. A flow signal <1.2 SDs above the mean decorrelation signal in the foveal avascular zone is generally considered as the avascular area.[29] However, there is no similar background reference available for the avascular area of the choriocapillaris layer.

This study demonstrated improvements in the central foveal zone's choroidal volume after PDT. This finding echoes with available studies that PDT improves choroidal thickness in CSC cases,[30] while the changes were first observed at 7 days and last for 30 days.[31] The current study showed a long-term effect in reduction of choroidal thickness for 6 months after PDT. Interestingly, PDT was reported to cause global changes influencing both the treated and untreated choroidal areas; however, the mechanism underlying this global effect remains unknown. In contrast to the reported literature, the current study only found significant improvements in the subfoveal choroidal thickness.

Our study may provide an insight into how different treatment modalities lead to fluid absorption in CSC. The PDT mechanism has been reported to cause short-term choriocapillaris hypoperfusion and long-term choroidal vascular remodelling. In contrast, subthreshold MLT works by stimulating and triggering the regeneration of the RPE, which leads to a long-term metabolic increase at the chorioretinal junction.[32] Thus, MLT was not considered to be able to alter the choriocapillaris plexus perfusion. The current study showed that PDT generated a more prominent effect in both choriocapillaris flow deficit area and choroidal thickness recovery than MLT. This result further supports the theory of PDT in being able to generate choroidal layer 'remodelling'.

This study has several limitations. First, choriocapillaris imaging by OCTA may provide information on the vascular status, but not reflect the actual choriocapillaris vascular flow because OCTA has inherent residual artefacts. There are possible artefacts from SRF and masking effects from the overlying pigment epitheliopathy in eyes with CSC. Therefore, the results should be interpreted with caution considering that the measured flow signal deficit areas do not truly correspond to absent choriocapillaris flow. Nonetheless, the flow deficit signals from OCTA images serve as an indirect reflection of real blood flow. Furthermore, this study adopted 3×3 mm OCTA scans centred on the fovea for analysis. A wider scan, such as 6×6 mm, may reveal flow signal reduction areas in other choroid areas. Also, artefacts are common in the presence of segmentation errors in choriocapillaris imaging.[33] All cases were included after careful inspection of the segmentation. There is no similar background reference available for the avascular area of the choriocapillaris layer. In addition, there is currently no consensus on the definition of cCSC. Many studies agree on adopting the definition of symptoms longer than 6 months,[34] while some studies on cCSC adopted duration of 3–6 months. Our study defined cCSC as patients suffering from symptoms longer than 3 months, with the range of the duration of symptoms from 4 to 12 months. Hence, some of the patients recruited here may arguably have resolved spontaneously, resulting in a bias for our study.

In summary, our study is the first randomised controlled trial to provide comprehensive assessment of the choroid. The eyes of patients with CSC had flow deficit areas in the choriocapillaris at baseline, which gradually improved after laser treatment. These findings suggest an underlying vascular alternation in the choriocapillaris of patients with CSC. Both PDT and MLT can promote choriocapillaris flow recovery; however, PDT has stronger choroidal remodelling effects.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This was a prospective, randomised controlled trial approved by the Clinical Research Ethics Committees of the New Territories East Cluster. Written informed consent was obtained from all participants. This study adhered to the tenets of the Declaration of Helsinki.

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Data availability statement All data summary relevant to the study are included in the article or uploaded as supplementary information. Original data files are available upon reasonable request.

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