

Subfoveal choroidal thickness after photodynamic therapy in patients with acute idiopathic central serous chorioretinopathy

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Background: The purpose of this study was to evaluate changes in subfoveal choroidal thickness after photodynamic therapy in patients with acute idiopathic central serous chorioretinopathy (ICSCR).

Methods: This was a retrospective observational study conducted in 63 participants. The primary outcome measure was subfoveal choroidal thickness at baseline and 3 days, one week, 4 weeks, and 12 weeks after photodynamic therapy. The secondary outcome measure was indocyanine green angiography at baseline and 4 weeks and 12 weeks after photodynamic therapy.

Results: Four weeks after photodynamic therapy, 20 (64.51%) symptomatic eyes showed hypofluorescence corresponding to the area of photodynamic therapy irradiation at the posterior pole. The mean subfoveal choroidal thickness increased significantly from $422 \pm 132 \mu\text{m}$ at baseline to $478 \pm 163 \mu\text{m}$ at day 3 after treatment ($P=0.022$) and then decreased to $362 \pm 113 \mu\text{m}$ at week 4 ($P<0.001$) and $339 \pm 135 \mu\text{m}$ at week 12 ($P<0.001$).

Conclusion: The subfoveal choroid in patients with acute ICSCR is thicker than in the normal population, and in symptomatic eyes is significantly thicker than in fellow eyes. Photodynamic therapy using a one third dose of verteporfin may decrease choroidal vascular hyperpermeability and choroidal thickness in patients with acute ICSCR.

Keywords: idiopathic central serous chorioretinopathy, photodynamic therapy, subfoveal choroidal thickness, indocyanine green angiography, optical coherence tomography, enhanced depth imaging

Introduction

Idiopathic central serous chorioretinopathy (ICSCR), first described by von Graefe in 1866, is characterized by idiopathic exudative detachment of the neurosensory retina in the posterior pole and one or more leaks from the retinal pigment epithelium. The precise pathophysiology of ICSCR is still unclear. Impairment in resorptive capacity and barrier function in retinal pigment epithelium was once considered to be an important contributing factor. However, Negi et al^{1,2} reported that simple dysfunction of retinal pigment epithelium could not lead to retinal detachment. Gass³ postulated that hyperpermeability of the choriocapillaris resulted in exudation of fluid into the subretinal space. Studies using indocyanine green angiography (ICGA) revealed that abnormalities of the choroidal vasculature, including hyperpermeability⁴⁻¹⁰ and venous congestion,¹⁰⁻¹² may be the essential elements of ICSCR.^{10,11} Other studies¹³ using high-resolution ultrasonography have also shown hyperdynamic circulation within the choroid of eyes with ICSCR.^{14,15}

Focal laser photocoagulation is a classic treatment for acute ICSCR, and can shorten the duration by about 2 months.¹⁶ However, whether it would reduce recurrence

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rates is controversial. A prospective, randomized clinical trial¹⁷ found that the final recurrence rate in a laser photocoagulation group was unchanged. Recurrent attacks always lead to widespread decompensation of retinal pigment epithelium and permanent vision loss. Photodynamic therapy can decrease hyperpermeability in the choroid and reduce leakage from retinal pigment epithelium, hence reducing the recurrence rate.^{18–22} Several studies^{23–25} have reported that photodynamic therapy has a dose-dependent effect, and that reducing the dose of verteporfin could diminish the adverse effects in the retina and choroid. Zhao et al²⁶ demonstrated that a 30% dose of verteporfin is safe and effective for acute ICSCR in Chinese patients.

The rapid development of imaging techniques has improved our understanding of the pathogenesis of ICSCR. Optical coherence tomography, which was invented in the late 1990s, has become an indispensable technique in evaluating and managing many ocular disorders. However, due to the signal loss occurring in the image path and the wavelength-dependent light scattering, conventional optical coherence tomography could not image the choroid clearly. Recently, Spaide et al²⁷ described commercially available enhanced depth imaging spectral-domain optical coherence tomography (EDI-OCT) which enables quantitative measurement of choroidal thickness and topography^{27–32} in various diseases, such as ICSCR,³³ myopia,³⁴ age-related macular degeneration,^{28,35} diabetes,³⁶ and glaucoma.³⁷

Maruko et al³⁸ reported that subfoveal choroidal thickness could be decreased using a half dose of photodynamic therapy in patients with ICSCR. In the current study, we performed EDI-OCT and ICGA in symptomatic eyes and fellow eyes of patients with acute ICSCR and evaluated the potential changes in subfoveal choroidal thickness after a 1/2 dose of photodynamic therapy in Chinese patients.

Materials and methods

Study design and patient recruitment

This retrospective observational study was performed in consecutive patients diagnosed with unilateral acute ICSCR at the Department of Ophthalmology, Yellow River Hospital, Henan University of Science and Technology, Sanmenxia, Henan Province, People's Republic of China, from July 2011 to March 2013. The study received approval from the institutional review board of Yellow River Hospital (approval number 2011-07-03). Written informed consent was obtained from all patients, and the procedures used followed the tenets of the Declaration of Helsinki. For the comparative study, a group of healthy sex-matched and age-matched (± 5 years)

subjects were recruited from our students, hospital staff, and families.

Diagnosis of acute ICSCR

All participants underwent the following clinical examination: best-corrected visual acuity, slit-lamp biomicroscopy, indirect ophthalmoscopy, fluorescein angiography, and ICGA (TRC-50DX/IMAGENet 2000; Topcon Medical Systems Inc, Tokyo, Japan). Acute ICSCR was diagnosed if patients had: subretinal fluid involving the macula associated with idiopathic leaks from the retinal pigment epithelium seen on fluorescein angiography; subretinal fluid confirmed by optical coherence tomography; and persistent serous retinal detachment for less than 6 months without widespread decompensation of the retinal pigment epithelium.

Inclusion and exclusion criteria

Inclusion criteria were: acute ICSCR; only a single eye with neurosensory retina or pigment epithelial detachment; age 20–70 years; and no spontaneous resolution after 3 months of conservative management. Exclusion criteria were: chronic ICSCR; a history of ocular disease, such as polypoidal choroidal vasculopathy, myopia, or age-related macular degeneration; a history of ocular surgery or photocoagulation; pregnancy; steroid use; and any other systemic disease.

Photodynamic therapy in acute ICSCR

The photodynamic therapy protocol was performed using a one third dose (2 mg/m²) of verteporfin (Visudine®; Novartis, Basel, Switzerland) to treat patients with acute ICSCR.²⁰ After intravenous administration of the 1/3 dose of verteporfin for 10 minutes, we then used a 689 nm laser system (Carl Zeiss, Dublin, CA, USA) to deliver an activating laser (dose 50 J/cm²) to the fundus of each patient. The exposure time was 83 seconds. The laser spot size was the diameter of the hyperpermeability region of ICGA plus 500 μ m.

Examination of subfoveal choroidal thickness

Subfoveal choroidal thickness was evaluated in the patients with acute ICSCR at baseline and 3 days, one week, 4 weeks, and 12 weeks after photodynamic therapy. The choroid was observed by EDI-OCT (Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany). The device was positioned close to the eye to obtain inverted images of the fundus, but the images were reinverted for display. Eye tracking was used during measurement. Seven sections, each containing 25 averaged raw scans, were obtained within a 5–30 degree

rectangle centered on the fovea. Choroidal thickness (defined as the zonal area between the inner scleral surface and the outer retinal pigment epithelium surface) was measured subfoveally on the transfoveal scan using the manufacturer's software (Heidelberg Eye Explorer version 1.6.1.0). Although the thickest section of the choroid might not be at the subfoveal region, in this study we measured the subfoveal choroidal thickness as an indicator to avoid selection bias. All measurements were performed independently by two experienced examiners. If the measurements differed by more than 15%, the examiners performed the measurement together twice.

Statistical analyses

All data was analyzed by PASW statistics version 18.0 (SPSS Inc, Chicago, IL, USA). The independent *t*-test, paired *t*-test, or least significant difference *t*-test was used to evaluate subfoveal choroidal thickness. Fisher's Exact tests were used to compare the difference in other clinical data. Results were considered to be statistically significant at *P*-values of 0.05.

Results

Baseline demographic characteristics

A total of 63 patients were finally enrolled, ie, 31 patients in the photodynamic therapy group and 32 patients in the control group. There was no statistically significant difference between the two groups with regard to mean age and sex (*P*=0.68 and *P*=0.78, respectively). The mean spherical equivalent refractive error in the photodynamic therapy group was -1.69 ± 2.24 diopters compared with -2.54 ± 1.96 diopters in the control group; the difference was statistically significant (*P*=0.02). The mean interval between onset of symptoms and treatment in the photodynamic therapy group was 45.74 ± 22.85 weeks (Table 1).

Table 1 Baseline demographic characteristics

	PDT group (n=31)	Control group (n=32)	P-value
Age (years)			
Mean \pm SD	45.63 \pm 6.24	47.24 \pm 5.93	0.68
Range	28–67	22–69	
Sex			
Male to female	26:5	27:5	0.78
Spherical equivalent refractive error (diopters)			
Mean \pm SD	-1.69 ± 2.24	-2.54 ± 1.96	0.02
Range	-3.50 to 2.75	-3.75 to 2.75	
Interval between onset of symptoms and treatment (weeks)			
Mean \pm SD	45.74 \pm 22.85	–	–
Range	28–62	–	–

Abbreviations: PDT, photodynamic therapy; SD, standard deviation.

Characteristics of ICGA

Of the 64 eyes from the 32 patients in the control group, ten (15.63%) had hyperfluorescence defined as choroidal vascular hyperpermeability in the middle phase of ICGA and 54 eyes (84.37%) did not have hyperfluorescence.

In the photodynamic therapy group, before treatment, 30 (96.78%) symptomatic eyes and 23 (74.19%) fellow eyes from 31 patients showed a mottling hyperfluorescence in the middle phase of ICGA. Four weeks after treatment, we found that 20 (64.51%) symptomatic eyes showed hypofluorescence corresponding to the area of photodynamic therapy irradiation at the posterior pole. The rate of choroidal vascular hyperpermeability in the fellow eye remained unchanged. This phenomenon persisted throughout the study.

Changes in subfoveal choroidal thickness

The mean subfoveal choroid thickness changes at baseline and follow-up are summarized in Tables 2, 3 and Figure 1. At baseline, the mean subfoveal choroid thickness in symptomatic eyes was significantly greater than in fellow eyes (422 ± 132 μ m and 367 ± 114 μ m, respectively, *P*=0.036). Mean subfoveal choroid thickness in the fellow eyes was significantly greater than in the control group (367 ± 114 μ m and 274 ± 53 μ m, respectively, *P*<0.001).

Based on the ICGA, the mean subfoveal choroid thickness of fellow eyes with hyperfluorescence was significantly greater than those without hyperpermeability (446 ± 105 μ m versus 279 ± 115 μ m, *P*<0.001). When comparing the difference between subfoveal choroidal thickness in the fellow eyes without hyperfluorescence and that in the control group, we found a negative result (279 ± 115 μ m versus 274 ± 53 μ m, *P*=0.520).

After photodynamic therapy, the mean subfoveal choroidal thickness increased significantly from 422 ± 132 μ m at baseline to 478 ± 163 μ m at day 3 (*P*=0.022) and then decreased to 362 ± 113 μ m at week 4 (*P*<0.001 versus baseline) and to 339 ± 135 μ m at week 12 (*P*<0.001 versus baseline, Figure 1). During follow-up, an interesting case occurred in the photodynamic therapy group (Figure 2).

Absorption of subretinal fluid

At successive follow-ups, the subretinal fluid in 19 patients decreased significantly at 4 weeks after photodynamic therapy, but not at day 3 and week 1. After 12 weeks of follow-up, the subretinal fluid in 25 patients was already fully absorbed.

Table 2 Subfoveal choroidal thickness at baseline

	PDT group			Control group (n=64)
	Symptomatic eyes (n=31)	Fellow eyes with hyperfluorescence in ICGA (n=23)	Fellow eyes with hyperfluorescence in ICGA (n=8)	
Mean ± SD	422±132	446±105	279±115	274±53
Range	136–642	331–642	136–372	97–335

Notes: Among-group comparison using Student's independent or paired *t*-tests. *P*-values < 0.05 are considered to be statistically significant.

Abbreviations: ICGA, indocyanine green angiography; PDT, photodynamic therapy; SD, standard deviation.

Safety

During follow-up, no adverse systemic or ocular events occurred.

Discussion

In the current study, we used EDI-OCT to evaluate changes in subfoveal choroid thickness after photodynamic therapy in patients with acute ICSCR. Our findings support the view that photodynamic therapy can decrease choroidal vascular hyperpermeability and choroidal thickness. Our findings also showed that the subfoveal choroid in patients with acute ICSCR was thicker than in healthy subjects, with the subfoveal choroid in symptomatic eyes being significantly thicker than in the fellow eyes. To our knowledge, this is the first study using EDI-OCT to quantitatively assess changes in subfoveal choroidal thickness after a one third dose of photodynamic therapy in a relatively large sample of patients with acute ICSCR.

Subfoveal choroidal thickness in healthy subjects has been reported to be between 261 µm and 354 µm.^{29,30,39–42} Our study showed that mean subfoveal choroidal thickness in the control group was 274 µm. The variation in results

Table 3 Subfoveal choroidal thickness during follow-up

	PDT group (symptomatic eyes, n=31)	PDT group (fellow eyes, n=31)
Choroidal thickness at baseline (µm)		
Mean ± SD	422±132	367±114
Range	136–642	113–573
Three days follow-up (µm)		
Mean ± SD	478±163	371±123
Range	157–668	121–569
Four weeks follow-up (µm)		
Mean ± SD	362±113	368±134
Range	112–574	108–581
Twelve weeks follow-up (µm)		
Mean ± SD	339±135	368±121
Range	108–578	115–575

Notes: Among-group comparison using Student independent or paired *t*-tests. *P*-values < 0.05 were considered to be statistically significant.

Abbreviations: PDT, photodynamic therapy; SD, standard deviation.

from the different studies may be attributable to variations in patient age, sex, axial length, and refractive condition, as well as the optical coherence tomography device used. Patient age^{28,30,40,43} has been recognized as the most influential factor in choroidal thickness. An EDI-OCT-based study undertaken by Margolis and Spaide³⁰ reported mean decreases in choroidal thickness of 15.6 µm per year in normal eyes. Ikuno et al⁴⁰ confirmed this finding. However, this theory might not suit for ICSCR patients. Imamura et al³³ reported that choroidal thickness did not correlate with age in ICSCR patients (*r*=0.15, *P*=0.43). Axial length is another important influencing factor. Li et al⁴² reported that subfoveal choroidal thickness decreased by 58.2 µm per mm increase in axial length adjusted for age and sex. Esmaeelpour et al⁴⁴ agreed with this view, and found that axial length was the most important determinant of choroidal thickness. Further, sex has been reported as another influential factor in choroidal thinning. In a multiple regression model,⁴² after adjustment for age and axial length, subfoveal choroidal thickness was on average 62 µm thicker in men than in women (95% confidence interval 21–104; *P*=0.0039). In contrast, Park and Oh⁴⁵ analyzed the association between sex and choroidal thickness, and found that the mean subfoveal thickness in males was 9 µm thicker than in females, but the difference was not significantly different (*P*>0.05). Moreover, an association between refractive condition and subfoveal choroidal thickness has also been reported. Ho et al⁴⁶ suggested that subfoveal choroidal thickness decreased by 6.205 µm for each diopter in patients with myopia. However, ICSCR patients are often hyperopic. In the current study, the mean spherical equivalent refractive error in the photodynamic therapy group was -1.69 ± 2.24 diopters compared with -2.54 ± 1.96 diopters in the control group; this difference reached statistical significance (*P*=0.02). This might be one reason why the subfoveal choroid in patients with ICSCR is thicker than in the normal population.

Most acute ICSCR is actually bilateral, even if subretinal fluid is active in one eye. Choroidal vascular hyperpermeability might have a crucial role in ICSCR. In an ICGA study,

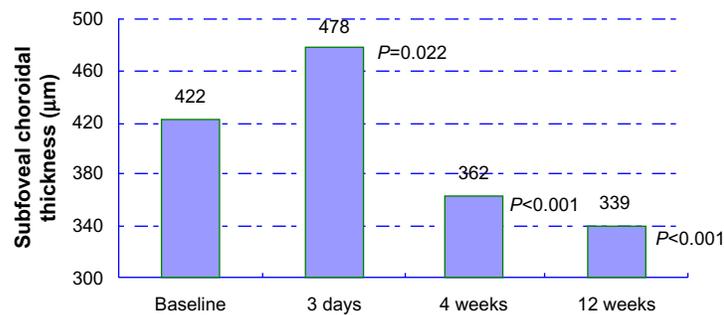


Figure 1 The changes of subfoveal choroidal thickness after photodynamic therapy.

Iida et al¹⁰ found that the incidence of choroidal vascular hyperpermeability was 62% in fellow eyes compared with 95% in symptomatic eyes. In the current study, 96.78% of symptomatic eyes and 74.19% of fellow eyes showed hyperfluorescence in the middle phase of ICGA in the photodynamic therapy group. This is similar to the findings of a study reported by Maruko et al.⁴⁷ Choroidal vascular hyperpermeability is always accompanied by choroid thickening in ICSCR patients. Imamura et al³³ reported that the choroid in patients with ICSCR was thicker bilaterally (including for symptomatic eyes and fellow eyes) than in normal eyes. In our study, the subfoveal choroid in symptomatic eyes was significantly thicker than in fellow eyes ($P=0.036$), and the subfoveal choroid in fellow eyes was significantly thicker than in age-matched and sex-matched control eyes ($P<0.001$). The subfoveal choroid thickness of the fellow eyes with hyperfluorescence in ICGA was significantly higher than that in those

without hyperpermeability ($P<0.001$). When we compared the difference between subfoveal choroidal thickness in the fellow eyes without hyperfluorescence and the control eyes, we found a negative result ($P=0.520$). These findings indicate that choroidal vascular hyperpermeability plays an important role in pathophysiology of ICSCR.

Photodynamic therapy with verteporfin, which has an occlusive effect in the choriocapillary layers, could decrease choroidal vascular hyperpermeability and subsequently choroidal thickness.^{18,21} Schlotzer-Schrehardt et al²⁴ and Schmidt-Erfurth et al²⁵ reported that photodynamic therapy has a dose-dependent profile. Increasing the dose of verteporfin or laser irradiation would increase the risk of vascular damage or cytotoxicity to the retina and choroid. It is important to balance the maximum therapeutic effect and the minimum complications. Half-dose photodynamic therapy³⁸ has been used widely to treat ICSCR, but might not be suitable for

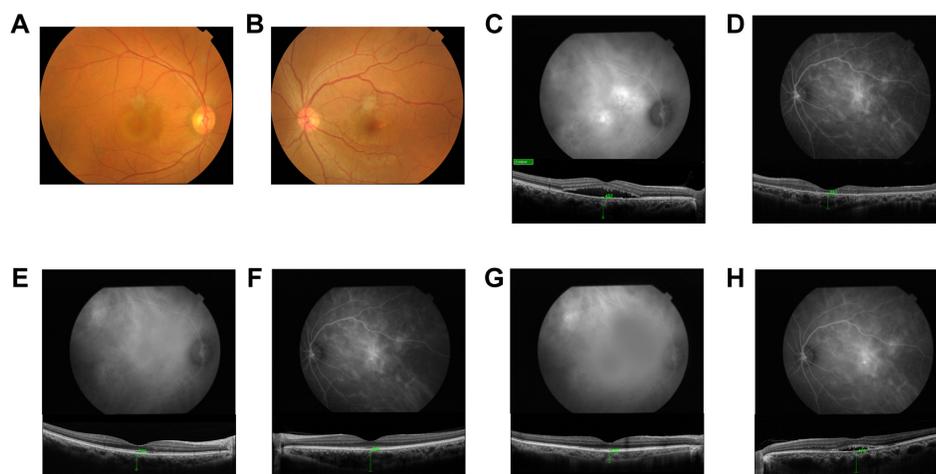


Figure 2 Case 1, a 36-year-old man with blurred vision in his right eye. (A) A fundus photograph of the right eye showing a serous retinal detachment at the fovea. (B) Fundus photograph of the left eye is normal. (C and D) ICGA showed bilateral choroidal vascular hyperpermeability in middle-phase. The subfoveal choroidal thickness at the baseline was 452 µm in the right eye and 351 µm in the left eye. (E and F) After PDT, the subfoveal choroidal thickness in his right eye decreased to 370 µm at week 4. However, the subfoveal choroidal thickness in the left eye increased to 494 µm, with ICGA indicating aggravation of his choroidal vascular hyperpermeability. (G and H) At week 11, in his left eye, ICGA showed aggravation of choroidal vascular hyperpermeability in middle-phase, with a subfoveal choroidal thickness of 470 µm.

Abbreviations: ICGA, indocyanine green angiography; PDT, photodynamic therapy.

Chinese patients. Zhao et al²⁶ used photodynamic therapy with various doses of verteporfin (70%, 60%, 50%, 40%, 30%, 20%, and 10% of the full dose) to manage ICSCR patients, and their results showed that 30% of the full dose of verteporfin was the lowest effective dose. In our study, following the recommendation of Zhao et al, we chose the 30% dose of verteporfin to manage our ICSCR patients. To our surprise, the mean choroidal thickness increased significantly from 422±132 µm at baseline to 478±163 µm at day 3. This transient increase in choroidal thickness may be a sign of increased exudation in the choroid. Eventually, after impairment of the choriocapillaris and vascular remodeling in the underlying choroid, the choroidal thickness decreased to 362±113 µm at week 4 and to 339±135 µm at week 12. Accompanying the changes in choroidal thickness, at week 4, we found that 64.51% of symptomatic eyes showed hypofluorescence corresponding to the area of photodynamic therapy irradiation at the posterior pole. Maruko et al³⁸ reported similar findings, ie, mean choroidal thickness increased from 389±106 µm at baseline to 462±124 µm ($P=0.008$) on day 2 after treatment, then reduced to 360±100 µm at week 1 and to 330±103 µm at week 4, with ICGA also showing decreased hyperpermeability. Maruko et al³⁸ used photodynamic therapy with a half dose (3 mg/m²) of verteporfin, which was higher than that (2 mg/m²) used in our study, but with similar efficacy. Recently, a prospective, nonrandomized, consecutive, open-label case series conducted by Uetani et al⁴⁸ reported an opposite outcome. In that study, Uetani et al compared the effects of a half-dose of verteporfin with those of a one-third dose of verteporfin for ICSCR. In the half-dose photodynamic therapy group, choroidal thickness reduced significantly from baseline. However, in the 1/3 dose photodynamic therapy group, choroidal thickness decreased in two eyes in which subretinal fluid disappeared, but did not change in the other eyes. However, only six patients were assigned to the photodynamic therapy group in that study, so the sample size was relatively small which might have led to bias.

Our retrospective study has some limitations. Acute ICSCR is well known to recur in some cases, so 3 months of follow-up seems to be short. A long-term study to evaluate the changes in subfoveal choroidal thickness and recurrence rate after photodynamic therapy is necessary. Additionally, the current EDI-OCT does not have automatic choroid segmentation software. Manual operation might lead to inaccuracy in some cases, so automatic choroid segmentation software is needed in future research. Moreover, the relationship between severity of hyperpermeability in ICGA and choroidal thickening should be investigated.

In conclusion, our findings revealed that: the subfoveal choroid in patients with acute ICSCR was thicker than in the normal population, with symptomatic eyes being significantly thicker than in fellow eyes; compared with half-dose or full-dose photodynamic therapy, a one-third dose of verteporfin could decrease choroidal vascular hyperpermeability and choroidal thickness in patients with acute ICSCR.

Disclosure

The authors report no conflicts of interests in this work.

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