

# FLUORESCEIN ANGIOGRAPHY-GUIDED PHOTODYNAMIC THERAPY WITH HALF-DOSE VERTEPORFIN FOR CHRONIC CENTRAL SEROUS CHORIORETINOPATHY

ARIF KOYTAK, MD, KAZIM EROL, MD, EROL COSKUN, MD,  
NIHAL ASIK, MD, HAKAN ÖZTÜRK, MD, YUSUF ÖZERTÜRK, MD

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**Purpose:** The purpose of this study was to evaluate the results of fluorescein angiography-guided photodynamic therapy with half-dose verteporfin in the treatment of chronic central serous chorioretinopathy with focal leakage areas.

**Methods:** Eight cases with a history of central serous chorioretinopathy of  $\geq 6$  months were included. All eyes had one or more focal areas of active retinal pigment epithelial leak. Photodynamic therapy was applied with half-dose verteporfin ( $3 \text{ mg/m}^2$ ), and the spot size was set limited to the area of active leakage shown on fluorescein angiography.

**Results:** The mean duration of the last central serous chorioretinopathy episode was 12.50 months. The mean best-corrected visual acuity improved from 20/122 to 20/60 the first month ( $P = 0.017$ ) and to 20/55 the first year after treatment ( $P = 0.018$ ). Seven eyes (87.5%) had improved vision 1 year after treatment, and 1 eye (12.5%) had stable vision with a mean number of 3.61 gained lines. The mean central macular thickness was reduced from  $366 \pm 95 \mu\text{m}$  to  $217 \pm 32 \mu\text{m}$  the first month ( $P = 0.006$ ).

**Conclusion:** Fluorescein angiography-guided photodynamic therapy with half-dose verteporfin seems to be a rational and effective alternative to other methods in the treatment of chronic central serous chorioretinopathy with focal leakage on fluorescein angiography.

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Central serous chorioretinopathy (CSC) is an idiopathic serous detachment of the neurosensory retina in the central macula region because of active retinal pigment epithelial (RPE) leakage. Although in the majority of cases, CSC is self-limiting and the final visual acuity is excellent, in  $\sim 5\%$  of the cases, the disease tends to become chronic with increased risk of developing progressive visual loss.

Despite recent progress in the understanding of the pathogenesis and advanced imaging techniques enabling diagnosis of every stage of the disease, there is

still no accepted, well-established treatment, particularly for the chronic forms of CSC. Fluorescein angiography (FA)-guided thermal laser photocoagulation applied focally to RPE leaks, or in a scattered manner, over diffuse areas of decompensating RPE has been reported to shorten the duration of the macular detachment. However, the long-term visual benefits of this treatment method are still debated, and risk of complications such as foveal burns, progressive pigment epithelial atrophy, and choroidal neovascularization limits its use in every case.

In recent years, photodynamic therapy (PDT) with verteporfin has been introduced as a new treatment option for chronic CSC, and several studies have shown beneficial visual and anatomical results in the majority of cases.<sup>1–6</sup> One possible mechanism of PDT in treating CSC is thought to be the result of capillary endothelial cell damage leading to choriocapillaris

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From the Kartal Training and Research Hospital, 2nd Eye Clinic, Istanbul, Turkey.

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Reprint requests: Arif Koytak, MD, Kartal Education and Research Hospital, 2nd Eye Clinic, Cevizli, Istanbul, Turkey; e-mail: akoytak@yahoo.com

narrowing and choroidal hypoperfusion, which in turn reduce choroidal exudation and induce choroidal vascular remodeling.<sup>5,7,8</sup> Another theory is that rapid accumulation of verteporfin in RPE cells because of their high lipid content and the expression of low-density lipoprotein receptors cause RPE cell damage at the site of laser application, which causes subsequent regeneration of RPE cells and recovery from the metabolic impairment at the RPE level.<sup>7</sup>

However, some complications such as the development of RPE atrophy, choriocapillaris ischemia, and secondary choroidal neovascularization have been reported after PDT for chronic CSC, applied with the standard protocol, after the infusion of full-dose verteporfin (6 mg/m<sup>2</sup>).<sup>3,5,9</sup> Moreover, various electrophysiological tests have shown that PDT causes transient impairment of retinal function.<sup>10–13</sup> These potential side effects might restrict the extensive use of PDT with the standard protocol in the treatment of chronic CSC. Because cytotoxicity and vascular damage associated with PDT are believed to be dosage-dependent, several modifications in the treatment parameters of PDT have been tried to minimize its potential side effects and enhance its efficacy.<sup>7,8</sup> Previous studies with modifications in verteporfin dosage and timing of laser application provided significant improvement in vision and reduced central macular thickness with no development of side effects.<sup>14,15</sup>

The aim of our study is to evaluate the 1-year results of FA-guided PDT with half-dose verteporfin in the treatment of chronic CSC with focal leakage areas. Our study protocol includes the application of PDT after the infusion of 3 mg/m<sup>2</sup> verteporfin with laser spot size limited to the area of active leakage on FA.

## Methods

A consecutive, nonrandomized series of cases with a history of CSC of  $\geq 6$  months was included in this retrospective study. The patients were recruited from Kartal Training and Research Hospital, Istanbul, Turkey, from November 2006 to March 2008.

This study included 8 patients (8 eyes) with a history of vision loss of  $\geq 6$  months caused by CSC diagnosed on fundus examination, optical coherence tomography (OCT), and fundus FA. All eyes had one or more focal areas of active RPE leak with subretinal fluid (SRF) and/or pigment epithelial detachment (PED) on OCT consistent with the clinical condition. Persistence of SRF and/or PED for at least 6 months, indicating chronic active disease, was documented with OCT. None had a history of thermal laser photocoagulation for the treatment of current or previous episodes of

CSC. Cases without demonstrable active focal areas of leakage on FA were not included in this study.

Written informed consents were obtained from all patients before the procedure. This study complied with the provisions of the Declaration of Helsinki.

All participants received a comprehensive ocular examination and special diagnostic evaluations before treatment. Eye examinations included Snellen best-corrected visual acuity (BCVA), refraction, slit-lamp biomicroscopy, applanation tonometry, and dilated fundus examination with a contact lens or a 90-diopter lens. These were followed by color- and red-free fundus photographs, digital FA, and OCT.

Photodynamic therapy was applied in the same manner as the treatment for neovascular age-related macular degeneration except that half the standard dose of verteporfin (3 mg/m<sup>2</sup> instead of 6 mg/m<sup>2</sup>) was administered, and the spot size was limited to the area of active leakage on FA. Timing of the laser application after drug infusion as well as duration and power of the infrared laser was kept unchanged (total light energy of 50 J/cm<sup>2</sup> and light dose rate of 600 mW/cm<sup>2</sup> for 83 seconds). The laser energy was applied with a spot size confined to the area(s) of active RPE leak with an additional 250  $\mu$ m covering the borders on each side. After treatment, protective spectacles were given, and patients were instructed to avoid direct sunlight or strong light for 3 days.

Patients had follow-up visits at the fourth day; first, third, and sixth months; and first year after treatment. Each follow-up visit included BCVA measurement, fundus examination, fundus photography, and macular OCT. In addition, control FAs were obtained on the third and sixth months after treatment.

The SPSS statistical software package, version 11.5 (SPSS, Inc., Chicago, IL) was used for data analysis. Snellen BCVA was converted to logarithm of the minimum angle of resolution (logMAR) BCVA and its corresponding line number for analysis. Serial comparisons of mean logMAR BCVA and OCT central foveal thickness were performed using the nonparametric Wilcoxon-signed rank test and two-tailed *t*-test, respectively.  $P \leq 0.05$  was considered statistically significant.

## Results

The demographic data and clinical findings of 8 eyes of 8 patients with chronic CSC are summarized in Table 1. The mean  $\pm$  standard deviation age of patients was  $40.75 \pm 7.25$  years (range, 33–56 years). Six patients were men (75%) and 2 were women (25%). The mean logMAR BCVA at presentation was  $0.69 \pm 0.27$  (range, 0.4–1.3), equivalent to the Snellen BCVA of 20/122 (range, 20/400–20/50).

Table 1. Demographic Data, Pre- and Posttreatment BCVA and CMT, and OCT Features of Eight Cases in This Study

Case No.	Sex	Age (Years)	Duration of CSC (Months)	BCVA			CMT on OCT			PDT Spot Size ( $\mu\text{m}$ )	OCT Features	Follow-Up (Months)
				Baseline	1 Month	12 Months	Baseline	1 Month	12 Months			
1	M	37	6	20/100	20/32	20/32	338	224	200	1450	SRF	12
2	M	42	12	20/100	20/32	20/25	428	189	165	4500	PED	12
3	M	37	6	20/100	20/32	20/20	550	216	186	1800	SRF	15
4	M	33	14	20/100	20/40	20/25	421	190	181	1950	SRF	23
5	F	42	34	20/400	20/200	20/200	291	236	215	1800	SRF	28
6	M	44	9	20/63	20/40	20/40	267	176	162	2600	SRF	16
7	M	56	7	20/63	20/63	20/63	289	275	257	1200	SRF + PED	24
8	F	35	12	20/50	20/40	20/32	345	231	189	1700	SRF	20

CMT, central macular thickness; M, male; F, female.

Three of the eyes had  $\geq 1$  previous episode of CSC, and the mean duration of the current episode was  $12.50 \pm 9.20$  months (range, 6–34 months). At the initial examination, six eyes had SRF alone without serous PED, one had combined SRF and PED, and one had isolated PED confirmed by FA and OCT.

Eyes with diffuse leakage on baseline FA were not included in this study. Thus, pretreatment FA showed CSC with focal leakage in all eyes, one with three actively leaking foci. Active leaking foci in all cases were localized between temporal vascular arcades.

The mean PDT laser spot size was  $2,125 \pm 1,042 \mu\text{m}$  (range, 1,200–4,500  $\mu\text{m}$ ). Two patients required a second PDT session 3 months after the first session.

At the first month after the PDT session, the mean logMAR BCVA improved from  $0.69 \pm 0.27$  to  $0.38 \pm 0.27$ . This increase in BCVA was statistically significant ( $P = 0.017$ ). The mean logMAR BCVA at the end of the first year was  $0.30 \pm 0.32$  (range, 0–1.0) and significantly different from the pretreatment BCVA ( $P = 0.018$ ). Seven eyes (87.5%) had improved vision 1 year after treatment with a mean number of 3.61 gained lines in Snellen scale. One eye (12.5%) had stable vision, whereas none of the eyes had decreased vision after the treatment.

Optical coherence tomography changes after PDT are summarized in Table 1. The mean central macular thickness at baseline was  $366 \pm 95 \mu\text{m}$  (range, 267–550  $\mu\text{m}$ ). One month after PDT, the mean central macular thickness reduced significantly to  $217 \pm 32 \mu\text{m}$  (range, 176–275  $\mu\text{m}$ ;  $P = 0.006$ ). Complete resolution of SRF at the macula was achieved in 6 of 8 eyes at the end of the first year (Figure 1). In one eye, a minimal serous PED persisted until the last control visit.

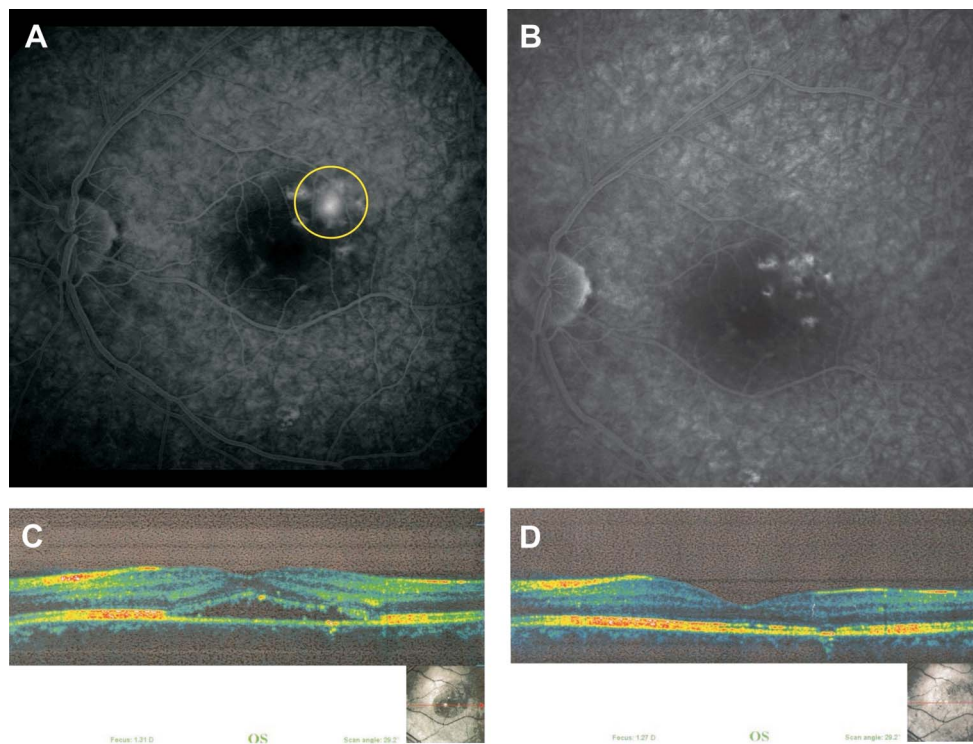
At month 3 after PDT, 5 eyes had absence of leakage, whereas 3 eyes had reduced but persistent leakage on FA. At the same visit, two eyes had SRF on

OCT. Only one eye had persistent dye pooling because of a minimal PED on the FA obtained at the sixth month. The mean number of PDT sessions required during the 1-year follow-up was 1.25. A single PDT session was sufficient to achieve treatment response in 6 eyes (75%). Two eyes required a second PDT session because of persistent SRF and leakage from the initial focus determined on the control OCT and FA.

Photodynamic therapy was tolerated well in all patients. None of the patients in this study group developed acute severe vision loss caused by PDT, infusion-site complications, photosensitivity reactions, or treatment-related systemic adverse effects. None of the patients had any subjective or objective loss of vision immediately after PDT or in the follow-up visits. Three patients described a relative scotoma corresponding to the site of PDT application. These scotomata disappeared in 2 cases before 3 months. A paracentral scotoma persisted in one patient and did not resolve throughout the follow-up period. A zone of choroidal hypoperfusion corresponding to the site of laser spot was observed in 3 cases in the FA at the 3-month control visit. The choroidal hypoperfusion in one of these cases persisted, and an associated RPE atrophy was observed in the 6-month control FA. Choroidal neovascularization was not detected in any of the cases throughout the follow-up period. None of the eyes had a recurrent CSC episode within the first year after treatment.

## Discussion

The pathogenesis of CSC is not yet fully understood. Both focal and diffuse impairment of RPE cells have been believed to be responsible for CSC.<sup>16,17</sup> However, more recent studies relying on indocyanine green angiography (ICGA) have shown that choroidal vascular hyperpermeability is a common feature of



**Fig. 1.** Left eye of patient 1. **A**, Pretreatment midphase FA showed focal leakage of fluorescein with multiple adjacent window defects. The yellow circle represents the laser spot size of 1,450  $\mu\text{m}$ . **B**, Posttreatment (3 months) midphase FA with no fluorescein leakage. **C**, Pretreatment OCT showed the presence of SRF. **D**, Posttreatment (3 months) OCT showed complete resolution of SRF.

CSC.<sup>18–21</sup> A possible explanation for the pathogenesis is that a focal increase in the permeability of the choriocapillaris overwhelms the RPE cells and causes mechanical breakdown of the RPE layer.<sup>22,23</sup> This defect or rip leads to serous leakage beneath the neurosensory retina and serous PED formation, characteristic of the CSC.<sup>24</sup> Especially in chronic CSC, prolonged detachment of the macula leads to progressive visual acuity deterioration and visual field damage caused by progressive and atrophic degeneration of RPE and photoreceptors. Unfortunately, there is no treatment for chronic CSC established by clinical trials. Until recently, the only treatment available for patients affected by chronic CSC was thermal laser photocoagulation, which could be directed to focal leaks,<sup>25</sup> with variable outcomes and complications such as scotomas, foveal burns, RPE atrophy, and choroidal neovascular membranes.

Recently, several studies have reported favorable outcomes with the use of PDT with a standard dose of verteporfin (6 mg/m<sup>2</sup>) for the treatment of CSC.<sup>1–6,26</sup> Piccolino et al<sup>3</sup> performed ICGA-guided PDT in 16 eyes with chronic CSC and reported complete resolution of serous retinal detachment 1 month after treatment in 75% of eyes. Three months after PDT, 69% of eyes had visual improvement of  $\geq 1$  line.<sup>3</sup> In

another study by Yannuzzi et al,<sup>4</sup> 20 eyes underwent ICGA-guided PDT, and treatment led to complete resolution of macular detachment in 60% of eyes with stable or improved vision in all eyes. In a study by Chan et al,<sup>5</sup> using standard-dose verteporfin PDT, 83% of eyes with chronic CSC were found to have visual improvement 3 months after PDT. In addition, Parodi et al<sup>1</sup> reported the use of PDT in one eye of one patient resulting in a successful outcome. They reported reduction of neurosensory detachment and subretinal lipid within 6 months and visual acuity improvement from 20/60 to 20/25, persistent 1 year after single PDT administration using verteporfin.<sup>1</sup> A similar finding was observed in a case report by Canakis et al.<sup>2</sup> In another case series reported by Taban et al,<sup>6</sup> PDT resulted in visual improvement in all 5 eyes within 1 month after PDT with a mean follow-up of 10 months.

Therefore, on the basis of these results, PDT with full-dose verteporfin seemed to be a beneficial treatment option for chronic CSC.

Despite the efficacy of PDT with full-dose verteporfin, potential complications might develop after treatment. Piccolino et al<sup>3</sup> reported development of secondary RPE changes in 31% of eyes, which were thought to be caused by hypoxic damage caused by choriocapillaris occlusion at the site of PDT. The

development of choroidal neovascularization after PDT for chronic CSC has also been reported in a case series by Chan et al<sup>5</sup> and a case report by Colucciello.<sup>9</sup> These potential side effects might be important considerations to restrict the extensive use of PDT for chronic CSC. Moreover, various electrophysiological tests such as multifocal electroretinography, pattern electroretinography, and electrooculography have stated that PDT might cause transient impairment of retinal function after treatment.<sup>10–13</sup> Cytotoxicity and vascular damage associated with PDT are believed to be dosage-dependent.<sup>7,8</sup> To enhance the efficacy of PDT in treating CSC while minimizing its side effects, Chan et al reduced the dosage of verteporfin and shortened the interval between infusion and laser application. Chan et al stated that their safety-enhanced protocol was as effective as previous studies using full-dose verteporfin PDT. This treatment regime resulted in significant improvement in BCVA and reduction in OCT central foveal thickness with complete resolution of serous retinal detachment in 89.6% of eyes. In addition, in a similar study, Lai et al<sup>14</sup> stated that PDT with half-dose verteporfin was effective with significant improvement in BCVA 1 month after treatment. In their study, 17 of 20 eyes (85%) had complete resolution of serous retinal detachment 1 month after PDT. In our study, we also applied PDT with half-dose verteporfin in the treatment of chronic CSC. None of the eyes in our group had visual loss, and the mean Snellen BCVA was improved from 20/122 to 20/60 within 1 month after treatment. Complete resolution of SRF and PED was observed in 75% of cases, and the mean foveal thickness was reduced from 366  $\mu\text{m}$  to 217  $\mu\text{m}$  within 1 month. These results were similar to previous studies of PDT with full- or half-dose verteporfin.

We also attempted to promote the safety of the procedure further by limiting the laser spot size to the focal area of leakage on FA. The rationale behind this was the fact that the active leaks observed on FA, rather than the areas of hyperfluorescence appearing on ICGA, are primarily indicative of symptomatic CSC. Although the presence of multifocal areas of choroidal vascular hyperpermeability during ICGA is a consistent finding of CSC, this is not a definitive marker of active disease. Several studies have shown that these areas of hyperfluorescence are found not only in correspondence with the leaking point seen on FA, but also in areas that appear clinically normal as well as unaffected fellow eyes. This is the reason why, unlike most of the studies using ICGA-guided PDT for the treatment of CSC, we preferred to use FA for determining the location of laser application. Mean laser spot size used in our study (2,125  $\mu\text{m}$ ) was

significantly smaller than the spot size used in the studies of Yannuzzi et al (6,395  $\mu\text{m}$ ), Lai et al (4,150  $\mu\text{m}$ ), and Chan et al (3,935  $\mu\text{m}$ ). Photodynamic therapy applied with smaller spot sizes after the infusion of half-dose verteporfin has provided therapeutic effects similar to previous studies with full-dose verteporfin and larger areas of application. It is possible that our treatment regime achieves sufficient therapeutic effect with less collateral damage to adjacent retinal and choroidal structures, which could increase the risk of PDT-associated complications and compromise the visual outcome.

One limitation for our proposed protocol, FA-guided PDT with half-dose verteporfin, was the subtype of chronic CSC with diffuse decompensation of RPE showing diffuse leakage on FA. For such cases of chronic CSC, which we excluded from our study group, ICGA guidance for PDT could be a more appropriate option for determining areas of laser application.

The main limitations of our study are the few cases, the lack of control groups of PDT with full-dose verteporfin and with ICGA guidance, and a placebo group for comparison. However, this study contributes to the concept that PDT is a promising modality in the treatment of chronic CSC, needing further research to clarify its application parameters and clinical value in the overall spectrum of CSC. In the authors' view, FA-guided PDT with half-dose verteporfin seemed to be a rational and effective alternative to other methods in the treatment of chronic CSC with focal leakage on FA.

**Key words:** central serous chorioretinopathy, photodynamic therapy, verteporfin.

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