EXTENDED REPORT

Safety enhanced photodynamic therapy with half dose verteporfin for chronic central serous chorioretinopathy: a short term pilot study

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Br J Ophthalmol 2006;90:869–874. doi: 10.1136/bjo.2006.090282

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Accepted for publication 9 March 2006

Aim: To evaluate short term safety of an enhanced photodynamic therapy (PDT) protocol with half dose verteporfin for treating chronic central serous chorioretinopathy (CSC).

Methods: 20 eyes of 18 patients with symptomatic chronic CSC underwent PDT using 3 mg/m² verteporfin. Verteporfin was infused over 8 minutes followed by indocyanine green angiography guided laser application 2 minutes later. Serial optical coherence tomography (OCT) and multifocal electroretinography (mfERG) recordings were performed before PDT, at 4 days, 2 weeks, and 1 month after PDT. The best corrected visual acuity (BCVA), OCT central retinal thickness, and mean mfERG response amplitudes and peak latencies were compared longitudinally. Subgroup analysis was further performed for eyes with or without pigment epithelial detachment (PED).

Results: At 1 month after PDT, the median BCVA improved from 20/40 to 20/30 ($p=0.001$). The mean central retinal thickness also reduced from 276 μm to 158 μm ($p<0.001$) and 17 (85%) eyes had complete resolution of serous retinal detachment and/or PED. mfERG showed no significant changes in the mean N1 and P1 response amplitude and latency for all eyes. Subgroup analysis demonstrated that eyes without PED had a significant increase in the mean central mfERG P1 response amplitude with reduction in P1 peak latency at 1 month post-PDT. For eyes with PED, transient reduction in the mean central P1 response amplitude was observed at 4 days post-PDT.

Conclusions: The modified safety enhanced PDT protocol with half dose verteporfin appeared to be a beneficial treatment option for patients with chronic CSC, especially in eyes without serous PED. Further controlled study is warranted to demonstrate the long term safety and efficacy of this treatment option.

Central serous chorioretinopathy (CSC) is characterised by the development of serous neurosensory retina detachment at the posterior pole.¹ In the majority of patients, CSC is self limiting and patients usually have good visual prognosis. However, in cases of chronic CSC, patients might develop progressive visual loss because of persistent serous retinal detachment, cystoid macular degeneration or retinal pigment epithelium (RPE) decompensation.^{2–3} With the use of indocyanine green angiography (ICGA), it has been demonstrated that CSC primarily affects the choroidal circulation and causes multifocal areas of choroidal vascular hyperpermeability.^{4–6}

In recent years, photodynamic therapy (PDT) with verteporfin has been performed in the treatment of chronic CSC and studies have demonstrated beneficial visual outcomes in the majority of patients.^{7–12} The mechanism of PDT in treating CSC is thought to be the result of choriocapillaris narrowing and choroidal hypoperfusion, leading to reduction of choroidal exudation and choroidal vascular remodeling.^{11–13–14} However, the use of PDT in the treatment of chronic CSC is not without complication as RPE atrophy and juxtafoveal choroidal neovascularisation (CNV) had been reported after PDT for chronic CSC.^{9–11} Moreover, with the use of multifocal electroretinography (mfERG), clinical and laboratory studies have demonstrated transient reduction in macular function following PDT.^{15–16} We postulated that the potential retinal damage caused by PDT might be minimised by reducing the dose of verteporfin, while at the same time having sufficient photodynamic effects on the choroidal vasculature required for treating CSC. The aim of this study is to evaluate the short term efficacy of a safety enhanced PDT protocol with half dose verteporfin in the treatment of

chronic CSC with the use of mfERG and optical coherence tomography (OCT).

PATIENTS AND METHODS

Study design and patient recruitment

This study was a non-randomised prospective case series carried out at the Department of Ophthalmology and Visual Sciences, Chinese University of Hong Kong. All patients with symptomatic chronic CSC of 3 months or more in duration were recruited from October 2004 to May 2005. Inclusion criteria included: (i) patients with best corrected visual acuity (BCVA) of 20/100 or better; (ii) presence of subretinal fluid (SRF) and/or serous pigment epithelial detachment (PED) on OCT; (iii) ability to maintain steady fixation for mfERG recording; and (iv) presence of abnormal dilated choroidal vasculature in ICGA. Patients who received previous PDT for chronic CSC or had evidence of CNV in fluorescein angiography were excluded. Informed consent was obtained from all subjects and the protocol was approved by the university's ethics committee.

Photodynamic therapy

PDT was performed using half the normal dose of verteporfin (Visudyne, Novartis AG, Bülach, Switzerland)—that is,

Abbreviations: BCVA, best corrected visual acuity; CNV, choroidal neovascularisation; CSC, central serous chorioretinopathy; ICGA, indocyanine green angiography; ISCEV, International Society for Clinical Electrophysiology of Vision; mfERG, multifocal electroretinography; OCT, optical coherence tomography; PDT, photodynamic therapy; PED, pigment epithelial detachment; RPE, retinal pigment epithelium; SRF, subretinal fluid

Figure 1 Left eye of patient 2. (A) Late phase fluorescein angiography with characteristic smoke-stack leakage at the central macula consistent with central serous chorioretinopathy (CSC). (B) Early phase indocyanine green angiography showing dilated choroidal vasculature characteristic of CSC. The red circle represents the laser spot size of 4400 μm applied for photodynamic therapy.

3 mg/m^2 infusion of verteporfin. Infusion of verteporfin was performed over 8 minutes followed by laser delivery at 10 minutes from the commencement of infusion. In patients with bilateral chronic CSC, sequential PDT was first performed on the eye with thicker OCT central retinal thickness, followed by laser application in the second eye. A total light energy of 50 J/cm^2 for 83 seconds was delivered to the area of choroidal hyperperfusion as observed in ICGA (fig 1). After treatment, protective spectacles were given and patients were instructed to avoid strong light for 3 days.

MfERG and OCT examinations

MfERG and OCT examinations were performed before PDT, at day 4, week 2, and month 1 after PDT. At each visit, BCVA was measured by certified optometrists and pupils were then dilated for mfERG and OCT examinations. MfERG was recorded using the Veris 4.8 clinic system (Electro-Diagnostic Imaging, San Mateo, CA, USA) with reference to the International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines.¹⁷ Multiple retinal areas were stimulated using an array of 103 hexagons with a binary m-sequence length of 2,¹⁴ displayed using a black and white monochrome cathode ray tube monitor. The overall stimulus pattern subtended an angle of approximately 25 degrees on either side of fixation. Luminances of the bright and dark hexagons were 200 cd/m^2 and 1 cd/m^2 , respectively. All subjects were light adapted in room light for 15 minutes before testing and light was maintained on during the recordings. Recordings were divided into 16 segments and obtained using Burien-Allen bipolar contact lens electrodes (Hansen Ophthalmic Laboratories, Iowa City, IA, USA). Patients' fixations were

monitored using a refractor/camera system and any segments with blinking, large eye movements, or fixation losses were discarded and recorded again. Retinal signals were filtered with low and high frequency cut-offs of 10 Hz and 300 Hz, respectively, and amplified with a gain of 100 000. OCT recordings were performed using an OCT 3 machine (StratusOCT, Carl Zeiss Meditec Inc, Dublin, CA, USA). Both vertical and horizontal scans of 6.0 mm centred on the fovea were obtained.

Data analysis

The first negative trough (N1) and first positive peak (P1) of the first order mfERG response amplitudes and peak latencies as well as the BCVA at the follow up visits were compared with baseline values using non-parametric Wilcoxon signed rank test. Individual mfERG responses for the hexagons were grouped into the two concentric areas centred on the fovea, with a central ring of 0–7 degrees (central group) and a peripheral ring of 7–25 degrees (peripheral group) as described previously.¹⁵ This grouping method allowed comparison of mfERG responses within the PDT treated central and the untreated peripheral areas.¹⁵ OCT central retinal thickness was measured manually using the retinal thickness mode and is defined as the distance between the inner surface of the RPE and the outer surface of the neurosensory retina at the fovea. Serial comparisons of OCT central retinal thickness was performed using two tailed *t* test. Statistical analysis was performed using SPSS v11.5. All eyes were analysed as a whole group with subgroup analyses performed for eyes with or without serous PED. A *p* value of ≤ 0.05 was considered statistically significant.

RESULTS

Baseline demographics

The demographic details of 20 eyes in 18 patients with chronic CSC in the study are displayed in table 1. The mean (SD) age of the patients was 46.0 (8.1) years (range 38–62 years). There were 17 males and one female. The median pre-PDT BCVA was 20/40 (range 20/20–20/100). Thirteen (65%) of the 20 eyes had one or more previous CSC episodes and the mean (SD) duration of the current episode was 6.7 (5.8) months (range 3–24 months). In all 13 eyes with previous CSC episode, there was evidence of RPE dysfunction with RPE atrophy observed in these cases. At baseline, 13 (65%) eyes had SRF without serous PED and seven (35%) eyes had both SRF and PED on OCT examination. Four eyes had subnormal OCT central retinal thickness of $<150 \mu\text{m}$ consistent with retinal atrophy associated with chronic or recurrent CSC.¹⁸ Two patients underwent bilateral sequential PDT (patients 6 and 17). The mean (SD) PDT laser spot size was 4150 (200) μm (range 4000–4600 μm). None of the patients developed any adverse event during verteporfin infusion or immediately after PDT.

Visual acuity changes after PDT

At day 4 and week 2 after PDT, the median BCVA improved from 20/40 to 20/30 but the improvement was not statistically significant at both visits (Wilcoxon signed rank test, $p = 0.85$ and $p = 0.20$, respectively). Two patients reported transient central scotoma within the first 2 days after PDT. Four weeks after PDT, the median BCVA was 20/30 and the improvement compared with baseline was statistically significant (Wilcoxon signed rank test, $p = 0.001$). All patients had subjective improvement in symptoms or BCVA at 1 month after PDT. Subgroup analysis showed significant improvement in BCVA at 1 month after PDT only in eyes without PED (Wilcoxon signed rank test, $p = 0.005$), while the improvement in BCVA for eyes with PED was not statistically significant (Wilcoxon signed rank test, $p = 0.063$).

Table 1 Demographic details, pre-PDT and post-PDT visual acuity, and OCT findings of 20 eyes of 18 patients in the study

Patient No	Age	Sex	Eye	Duration of symptoms (months)	No of CSC episode	Baseline BCVA	BCVA at 1 month post-PDT	Baseline OCT foveal thickness (μm)	OCT foveal thickness at 1 month (μm)	Baseline OCT anatomical findings
1	43	Male	Right	24	3	20/40	20/30	208	125	SRF
2	60	Male	Left	3	2	20/50	20/50	260	159	PED + SRF
3	51	Male	Left	3	2	20/50	20/25	485	149	SRF
4	52	Male	Left	3	3	20/30	20/20	297	149	SRF
5	41	Male	Right	4	1	20/40	20/30	334	271	SRF
6A	39	Male	Left	6	2	20/25	20/20	188	121	PED + SRF
6B	39	Male	Right	6	2	20/25	20/20	465	121	PED + SRF
7	58	Male	Right	3	1	20/70	20/40	315	110	SRF
8	39	Male	Left	3	2	20/30	20/30	278	117	SRF
9	40	Female	Left	5	1	20/50	20/30	208	214	SRF
10	39	Male	Left	3	4	20/25	20/20	319	133	SRF
11	39	Male	Right	4	1	20/20	20/18	173	126	SRF
12	41	Male	Left	12	1	20/70	20/30	119	102	SRF
13	38	Male	Left	18	4	20/50	20/30	398	190	SRF
14	44	Male	Right	5	3	20/25	20/25	110	114	PED + SRF
15	39	Male	Right	3	1	20/30	20/30	600	292	SRF
16	52	Male	Right	3	3	20/40	20/40	130	201	PED + SRF
17A	62	Male	Right	11	2	20/70	20/50	124	114	PED + SRF
17B	62	Male	Left	11	2	20/100	20/70	243	231	PED + SRF
18	51	Male	Right	3	1	20/25	20/25	258	125	SRF

CSC, central serous chorioretinopathy; BCVA, best corrected visual acuity; OCT, optical coherence tomography; SRF, subretinal fluid; PED, pigment epithelial detachment.

Changes in OCT central foveal thickness (table 2)

For the entire group and for the subgroup of patients without PED, there were significant reductions in central foveal thickness at week 2 and month 1 after PDT (two tailed *t* test, $p=0.001$). Seventeen (85%) of the 20 eyes had complete resolution of SRF and/or PED at 1 month post-PDT. For the seven eyes with both SRF and PED, there was a mild increase in central foveal thickness at day 4 post-PDT, which subsequently reduced at week 2 and month 1 after PDT. The changes however were not statistically significant at all follow up visits. Examples of the OCT and mfERG changes are displayed in figures 2 and 3.

Changes in mfERG response amplitudes (table 3)

There were no significant changes in the mean N1 and P1 mfERG response amplitudes for both the central and peripheral groups at all follow up visits for all 20 eyes in the study. For the 13 eyes without PED, no significant

changes in the N1 and P1 response amplitudes were observed at day 4 and week 2 after PDT. At 1 month after PDT, there was significant increase in the mean P1 retinal response amplitude of the central group compared with baseline (Wilcoxon signed rank test, $p=0.039$). No significant changes for the mean N1 and P1 response amplitude of the peripheral group were observed compared with baseline. For the seven eyes with PED, there was significant reduction in the mean central P1 response amplitude at day 4 post-PDT (Wilcoxon signed rank test, $p=0.043$). The transient reduction in mean central P1 response amplitude recovered by week 2 and no significant change was observed.

Changes in mfERG peak latencies (table 4)

For all 20 eyes, no significant changes in the mean N1 and P1 response latencies for both the central and peripheral groups were observed at day 4 and week 2 after PDT. There was statistically significant reduction in P1 peak latency for the

Figure 2 Trace array (top) and response density plot (middle) of multifocal electroretinogram and optical coherence tomography (bottom) of a 51 year old man with central serous chorioretinopathy (patient 3). (A) Pretreatment mfERG demonstrated central reduction of retinal responses and OCT showed the presence of subretinal fluid without pigment epithelial detachment at the central macula. (B) Four days after PDT, there were no significant changes in either mfERG and OCT findings. (C) At 1 month after PDT, there was significant increase in mfERG responses with complete resolution of subretinal fluid on OCT.

Figure 3 Trace array (top) and response density plot (middle) of multifocal electroretinogram and optical coherence tomography (bottom) of a 60 year old man with central serous chorioretinopathy (patient 2). (A) Pretreatment mfERG demonstrated central reduction of retinal responses and OCT showed the presence of shallow subretinal fluid with serous pigment epithelial detachment (PED) at the central fovea. (B) Four days after PDT, OCT demonstrated an increase in the extent of the serous PED with mild reduction in the central mfERG response amplitude. (C) At 1 month after PDT, there was complete resolution of the serous PED and subretinal fluid on OCT with associated increase in mfERG response amplitude.

central group at 1 month after PDT (Wilcoxon signed rank test, $p = 0.032$). For the 13 eyes without PED, no significant changes in the mean N1 and P1 response latencies for both the central and peripheral groups were observed at 4 days after PDT. There were significant reductions in the mean P1 peak latencies at both week 2 and month 1 post-PDT visits (Wilcoxon signed rank test, $p = 0.041$ and $p = 0.027$ respectively). The differences in peak latencies of peripheral groups were not significant at all visits. No significant changes in both the N1 and P1 peak latencies of the central and peripheral groups were observed for eyes with PED at all follow up visits.

DISCUSSION

Several studies have reported a favourable outcome when using PDT with a standard dose of verteporfin (6 mg/m^2) for treating chronic CSC.⁷⁻¹² In the study by Cardillo Piccolino *et al*, ICGA guided PDT resulted in complete resolution of serous retinal detachment 1 month after treatment in 75% of eyes, with 69% of eyes having visual improvement 3 months after PDT.⁹ However, in 31% of eyes, secondary RPE changes developed at the site of PDT which were thought to be the result of hypoxic damage caused by choriocapillaris occlusion.⁹ In another study, we also observed the development of juxtafoveal CNV 3 months after PDT with full dose verteporfin for treating chronic CSC.¹¹ These side effects of PDT might be potentially important drawbacks in treating patients with chronic CSC as they generally have better vision compared with patients with CNV. Moreover, the use of mfERG has also demonstrated that PDT might result in

transient impairment in retinal function following treatment.^{15, 16} In order to enhance the efficacy of PDT in treating CSC while minimising its side effects, we reduced the dosage of verteporfin and shortened the interval between infusion and laser application. As the mechanism of PDT in CSC is caused by reducing the choroidal hyperpermeability, a lower dosage of verteporfin might be sufficient to induce choroidal vascular remodelling after PDT. A previous study has demonstrated that the maximal concentration of verteporfin within the choroidal circulation is achieved at 10 minutes following infusion, while the concentration at the retinal outer segment is still relatively low.¹⁹ Shortening the interval between the infusion and laser application might therefore minimise any collateral damage to adjacent retinal structures.

In this study, we demonstrated that PDT with half dose verteporfin resulted in significant improvement in BCVA at 1 month after PDT. The improvement in BCVA was associated with reduction in OCT central retinal thickness. Overall, 17 (85%) of the 20 eyes had complete resolution of serous retinal detachment at 1 month after PDT and the result compared favourably with the rates of 60% to 83% reported in previous studies using full dose verteporfin.¹⁰⁻¹² Subgroup analysis showed that significant reduction in central retinal thickness occurred only in eyes without PED as the reduction in central retinal thickness was not statistically significant for the seven eyes with PED. With the use of mfERG, we also demonstrated that significant increase in central P1 response amplitude and significant reduction in central P1 peak latency at 1 month after PDT for

Table 2 Changes in central retinal thickness before and after PDT				
	Mean central retinal thickness (SD) (µm)			
	Pre-PDT	4 days post-PDT	2 weeks post-PDT	1 month post-PDT
All eyes (n = 20)	276 (132)	293 (144)	191 (75)	158 (56)
p value*		0.49	0.001	0.001
SRF without PED (n = 13)	307 (130)	303 (130)	198 (83)	161 (62)
p value*		0.85	0.001	0.001
SRF with PED (n = 7)	217 (124)	275 (176)	179 (124)	152 (47)
p value*		0.38	0.43	0.24

*Two tailed *t* test (compared with pre-PDT).

Table 3 Mean central and peripheral N1 and P1 response amplitudes

	Mean response amplitude (SD) (nV/deg ²)			
	Pre-PDT	4 days post-PDT	2 weeks post-PDT	1 month post-PDT
All eyes (n = 20)				
Central N1	13.88 (4.98)	13.65 (5.51)	13.70 (4.13)	14.64 (5.77)
p Value*		1.00	0.90	0.63
Peripheral N1	8.87 (2.61)	8.29 (2.40)	8.62 (2.42)	8.75 (2.68)
p Value*		0.06	0.13	0.70
Central P1	39.72 (14.12)	39.15 (15.74)	40.06 (12.39)	42.91 (16.08)
p Value*		0.92	0.65	0.22
Peripheral P1	26.88 (8.20)	25.11 (8.01)	26.88 (8.20)	26.43 (8.66)
p Value*		0.14	0.26	0.58
SRF without PED (n = 13)				
Central N1	14.26 (2.82)	15.58 (4.73)	14.69 (2.77)	16.38 (4.75)
p Value*		0.20	0.35	0.16
Peripheral N1	9.45 (1.65)	9.19 (1.77)	9.22 (1.30)	9.83 (1.14)
p Value*		0.33	0.31	0.35
Central P1	41.65 (11.98)	44.75 (14.68)	43.33 (10.14)	48.82 (12.27)
p Value*		0.21	0.17	0.039
Peripheral P1	29.61 (6.03)	28.38 (6.81)	28.98 (6.03)	30.31 (4.42)
p Value*		0.26	0.18	0.70
SRF with PED (n = 7)				
Central N1	13.15 (7.86)	10.06 (5.32)	11.86 (5.71)	11.40 (6.46)
p Value*		0.14	0.31	0.15
Peripheral N1	7.79 (3.75)	6.60 (2.63)	7.50 (3.60)	6.73 (3.60)
p Value*		0.08	0.31	0.19
Central P1	36.13 (17.92)	28.76 (12.62)	33.99 (14.62)	31.93 (17.36)
p Value*		0.043	0.31	0.18
Peripheral P1	21.80 (9.71)	19.01 (6.62)	22.30 (9.90)	19.21 (10.26)
p Value*		0.31	0.74	0.19

*Wilcoxon signed rank test (compared with pre-PDT).

eyes without PED. Based on these findings, it appeared that PDT using half dose verteporfin may be more effective in treating chronic CSC eyes without PED. The difference in responses to PDT in cases with or without PED might be because of more severe RPE damage or differences in pharmacokinetics in cases with PED, as it had been shown that CNV associated with serous PED had a poorer response

after PDT.²⁰ Further research to evaluate the differences in treatment response is justified.

Using a reduced dose of verteporfin, we did not observe any significant reduction in mfERG response amplitude or delay in peak latencies after PDT when all eyes were analysed. The result differed from our previous study in which transient reductions in retinal response amplitudes

Table 4 Mean central and peripheral N1 and P1 peak latencies

	Mean peak latency (SD) (ms)			
	Pre-PDT	4 days post-PDT	2 weeks post-PDT	1 month post-PDT
All eyes (n = 20)				
Central N1	14.29 (1.09)	14.65 (1.19)	14.30 (1.40)	14.17 (0.90)
p Value*		0.28	0.68	0.42
Peripheral N1	14.25 (1.14)	14.46 (1.16)	14.13 (1.20)	14.29 (0.95)
p Value*		0.24	0.54	0.81
Central P1	27.62 (1.59)	28.00 (2.14)	27.12 (1.92)	27.04 (1.26)
p Value*		0.36	0.072	0.032
Peripheral P1	26.79 (1.74)	27.01 (1.85)	26.92 (1.78)	27.00 (1.52)
p Value*		0.12	0.47	0.39
SRF without PED (n = 13)				
Central N1	14.23 (1.19)	14.61 (1.12)	14.18 (0.77)	14.22 (0.87)
p Value*		0.35	0.90	0.83
Peripheral N1	14.17 (1.27)	14.35 (1.18)	13.85 (0.81)	14.17 (0.96)
p Value*		0.26	0.13	1.00
Central P1	27.49 (1.77)	27.76 (1.97)	26.92 (1.49)	26.72 (1.15)
p Value*		0.34	0.041	0.027
Peripheral P1	26.54 (1.76)	26.68 (1.63)	26.55 (1.23)	26.54 (1.26)
p Value*		0.23	0.57	0.95
SRF with PED (n = 7)				
Central N1	14.40 (0.93)	14.74 (1.41)	14.53 (2.21)	14.06 (1.01)
p Value*		0.68	0.49	0.083
Peripheral N1	14.40 (0.93)	14.64 (1.18)	14.64 (1.65)	14.51 (0.95)
p Value*		0.41	0.46	0.56
Central P1	27.86 (1.27)	27.86 (2.53)	27.50 (2.62)	27.63 (1.32)
p Value*		0.68	0.50	0.59
Peripheral P1	27.26 (1.73)	27.74 (2.21)	27.61 (2.49)	27.86 (1.68)
p Value*		0.19	0.47	0.13

*Wilcoxon signed rank test (compared with pre-PDT).

were observed at day 4 and week 2 after full dose PDT.¹⁵ Therefore, it appears that transient impairment of retinal function might be reduced using half dose PDT in treating chronic CSC. Despite the apparent safety in terms of lack of mfERG reduction, two patients still reported the development of central scotoma for the first 2 days after treatment. Moreover, subgroup analysis also revealed a significant reduction in the mean central P1 response amplitude for eyes with PED at day 4 post-PDT. Therefore, it appeared that transient impairment in retinal function might still occur following half dose PDT in eyes with serous PED and PDT should therefore be used more cautiously in these cases.

The main limitation of this study is the lack of a control group using full dose verteporfin or observation control group. Another limitation was the small number of cases, especially in the subgroup analysis. Thirdly, the short duration of follow up in the study is another limitation and the recurrence rate and safety of this modified treatment protocol will require further evaluation. Moreover, a future study might consider another approach to minimise potential side effects of PDT, including reducing laser energy as performed in the Visudyne in Minimally Classic CNV study.²¹ None the less, the results from this pilot study using the safety enhanced PDT protocol with half dose verteporfin for treating chronic CSC appeared quite promising, especially for eyes without PED as there was significant improvement in visual acuity as well as in OCT and mfERG findings. In view of these encouraging results, a randomised placebo controlled clinical trial is warranted for evaluating the efficacy of this modified safety enhanced PDT regime with half dose verteporfin in treating patients with chronic CSC.

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Financial support: nil.

We declare that we have no conflicting financial interest.

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