Microperimetric Changes After Photodynamic Therapy for Central Serous Chorioretinopathy

FEVZİ SENTURK, MURAT KARACORLU, HAKAN OZDEMİR, SERRA ARF KARACORLU, AND OMER UYSAL

• PURPOSE: To evaluate the effect of half-dose verteporfin photodynamic therapy (PDT) on macular function in cases of central serous chorioretinopathy (CSC).
• DESIGN: Interventional case series.
• METHODS: A total of 24 eyes from 24 cases of CSC were included in this study. In each eye, at baseline and 1, 3, and 6 months after half-dose PDT, logMAR best-corrected visual acuity (BCVA); central 10-degree, 20-degree, and paracentral 10-degree to 20-degree retinal sensitivity; and also mean retinal sensitivity results for each case over the area that was treated with half-dose PDT (PDT spot area) by MP-1 microperimetry and optical coherence tomography (OCT) foveal morphologic changes were assessed. The MP-1 microperimetry sensitivity map was overlaid onto an indocyanine green angiography image recorded on a Heidelberg scanning laser ophthalmoscope using dedicated MP-1 software to evaluate the PDT laser spot area.
• RESULTS: After treatment, BCVA and central 10-degree, 20-degree, paracentral 10-degree to 20-degree, and PDT laser spot area retinal sensitivity were improved significantly. In OCT in 20 of 24 eyes (83%), subretinal fluid (SRF) was resolved 1 month after half-dose PDT. At 3 and 6 months after treatment, SRF was resolved at all eyes. None of the patients in this study developed any systemic or ocular adverse events associated with verteporfin treatment.
• CONCLUSION: Half-dose verteporfin PDT induced a significant increase in central 10-degree, 20-degree, paracentral 10-degree to 20-degree, and also PDT laser spot area retinal sensitivity over 6 months in cases of CSC. (Am J Ophthalmol 2011;151:303–309. © 2011 by Elsevier Inc. All rights reserved.)

CENTRAL SEROUS CHORIORETINOPATHY (CSC), WHICH is characterized by focal serous retinal detachment in the macular area, is often accompanied by pinpoint leakage from the retinal pigment epithelium (RPE) that is seen on fluorescein angiography.[1] Best-corrected visual acuity (BCVA) is often only moderately decreased, and can be improved with the addition of a small hyperopic correction. In most cases, CSC is self-limited and resolves spontaneously over 4 to 6 months, albeit with mild color- or contrast-sensitivity alterations.[2] In approximately 30% to 50% of cases, there may be recurrence, and patients may even experience visual loss with BCVA of 20/200 or worse because of chronic neurosensory retinal detachment and RPE atrophy.[3] With the use of indocyanine green angiography, it has been demonstrated that CSC primarily affects the choroidal circulation and causes multifocal areas of choroidal vascular hyperpermeability.[4,5]

There have been several reports that appear to show that photodynamic therapy (PDT) is an effective treatment for chronic CSC.[6–12] In these studies BCVA is the standard way to measure visual performance, but it does not describe the full extent of the functional impact on visual performance in patients with compromised central visual fields attributable to chronic CSC. Evaluation of retinal sensitivity and central retinal field function using microperimetry, which is 1 of the functional evaluation techniques, is more informative than BCVA testing alone.[13–15] The value of testing macular function by central microperimetry in chronic CSC has been shown extensively.[13,14] MP-1 microperimetry allows automated functional analysis of the macula associated with real-time correction of eye movements. The procedure provides exact localization of the tested region on the retina, even in patients with unstable fixation. Microperimetry is also a valuable tool in evaluating the safety of new therapeutic strategies. Improved or stable retinal sensitivity and visual fields are important indicators of the absence of treatment-induced toxic effects.

In this study we evaluated changes in functional macular mapping obtained by the MP-1 microperimeter in patients with chronic CSC during a 6-month follow-up of half-dose PDT therapy.

METHODS

ALL CASES OF SYMPTOMATIC CHRONIC CSC OF 4 MONTHS or more in duration were recruited to the study. Inclusion criteria included BCVA of 20/200 or better, presence of subretinal fluid (SRF) on optical coherence tomography (OCT), and presence of abnormal dilated choroidal vasculature on indocyanine green angiography. Patients were excluded who had received previous PDT for chronic CSC

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TABLE 1. Clinical Characteristics of Cases of Central Serous Chorioretinopathy Before and After Half-Dose Photodynamic Therapy

Patient	Age (Years)	Visual Acuity (logMAR)				Central 20-Degree Retinal Sensitivity (dB) by MP-1 Microperimetry				Photodynamic Therapy Laser Spot Size (μm)
		Baseline	1 Month	3 Months	6 Months	Baseline	1 Month	3 Months	6 Months	
1	49	0.4	0.1	0.1	0.1	10.3	13.1	14.4	14.5	2500
2	37	0.2	0.1	0	0	10.1	10.8	14.9	17.8	2900
3	45	1	0.7	0.7	0.5	9.5	11.9	11	11.2	3300
4	55	1	1	1	0.8	4.6	5	5.3	9.7	2000
5	44	0.3	0.3	0.3	0.3	6.5	11.6	10.3	10.8	1800
6	47	0.7	0.7	0.7	0.7	6.3	7.8	8.2	8	3200
7	42	0.5	0.5	0.3	0.3	12.7	13.9	14.1	14.3	2300
8	55	1	1	1	1	5.7	6.6	7	7.8	2400
9	45	0.7	0.5	0.5	0.3	5.4	10.1	9.9	13.3	3000
10	52	1	1	1	1	6.6	8.2	8.3	8.8	3300
11	44	0.3	0.3	0.2	0.2	14.7	15.7	15.6	16.2	2400
12	55	0.5	0.3	0.3	0.2	14	14.2	15.2	15.3	2100
13	55	0.3	0.1	0.1	0.2	12.3	13.3	13.6	14	2700
14	44	0.5	0.5	0.5	0.5	7.9	10.8	13.4	13.5	2500
15	45	0.1	0	0	0	13.6	14.3	15.2	15.3	1700
16	55	0.3	0.1	0	0	12.9	15.3	17.4	16.6	2600
17	45	0.1	0	0	0	12.8	14.2	16.7	16	2300
18	54	0.5	0.3	0.2	0.2	5.7	7	8.8	8.5	1900
19	53	0.3	0.2	0.1	0.2	16.1	16.7	16.5	16	2700
20	35	0.3	0.3	0.3	0.3	14.2	16.2	16.5	16.3	2300
21	42	0.3	0.2	0	0	12.2	15.8	15.6	15.7	2100
22	34	0.3	0	0	0	13	16.7	17.1	16.9	2700
23	50	0.3	0.2	0	0	13	15	15.4	15.5	2400
24	36	0.3	0	0	0	12.4	17	18.4	17.7	3000
Mean ± SD	46 ± 6	0.47 ± 0.28	0.35 ± 0.32	0.30 ± 0.34	0.28 ± 0.31	10.52 ± 3.53	12.55 ± 3.56	13.28 ± 3.71	13.74 ± 3.21	2500 ± 455
P[a]			<.001	<.001	<.001		<.001	<.001	<.001	

dB = decibel; logMAR = logarithm of the minimal angle of resolution; SD = standard deviation.

[a]Compared with pretreatment by repeated analysis of variance and Bonferroni post hoc test.

TABLE 2. Mean Retinal Sensitivity over the PDT area.[a] (n = 24)

	Baseline	1 Month	3 Months	6 Months
MP-1 microperimetry sensitivity over the PDT area[a] (dB)	7.41 ± 4.29	10.39 ± 4.45[b]	11.72 ± 4.53[a]	12.23 ± 4.07[a]

dB = decibel; PDT = photodynamic therapy.
[a]PDT area = The area treated with half dose verteporfin photodynamic therapy.
[b]$P < .001$ by repeated analysis of variance and Bonferroni post hoc test.

or had evidence of choroidal neovascularization (CNV) on fluorescein angiography, corneal opacity, a history of ocular surgery, glaucoma or ocular hypertension, a history of intraocular inflammation such as anterior or posterior uveitis, multifocal choroiditis, a history of retinal detachment, a history of ocular trauma, a history of steroid usage and optic neuropathy, or refractive error more than ±6.00 diopters. All patients underwent a complete ophthalmic examination, including BCVA, indirect ophthalmoscopy, fluorescein and indocyanine green angiography, microperimetry, and OCT. BCVA in each eye was measured at 4 meters with Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol with modified ETDRS distance chart transilluminated with a chart illuminator (Precision Vision, Bloomington, Illinois, USA). Vision results were quantified as logMAR units. Fluorescein and indocyanine green angiography were performed on a Heidelberg scanning laser ophthalmoscope (Heidelberg Engineering, Heidelberg, Germany). OCT scans were recorded on an OCT 3000 scanner (Carl Zeiss Ophthalmic System, Humphrey Division, Dublin, California, USA).

Macular sensitivity was evaluated by MP-1 microperimetry (Nidek, Vigonza, Italy). The MP-1 provides a 45-degree nonmydriatic view of the fundus with automated correction for eye movements. Goldmann III stimuli and a 4-2-1 staircase strategy were used, and a circular test grid with 74 stimulus locations covering an area of 20 degrees was applied. The microperimetry sensitivity map was also overlaid onto other images using dedicated MP-1 software. This software allows for the exact superimposition of sensitivity data to different images separately (infrared, autofluorescence, fluorescein and indocyanine green angiography). The superimposition is obtained by the semiautomatic detection of 2 identical anatomic landmarks on both images. This software has previously been tested for validity and repeatability.[16] To assess microperimetry results over the area that was treated with PDT, we superimposed sensitivity data on the indocyanine green angiography image of the Heidelberg scanning laser ophthalmoscope.

The mean retinal sensitivities at the 28 locations (number of measurement points) covering the central 10-degree field, 76 locations covering the central 20-degree field, and 48 locations covering the paracentral 10-degree to 20-degree field, and number of measurement points and mean retinal sensitivity results for each patient over PDT area were determined. The stimuli were projected on a white background with background illumination set to 1.27 cd/m^2 and a stimulus presentation time of 200 ms. The fixation target was varied in size (2-degree or 4-degree red cross) according to the patient's BCVA. All patients had to demonstrate good collaboration in the microperimetry test, which means a prompt and correct understanding of the technique and a good capacity for concentration. Each patient underwent a preliminary practice test prior to the definitive microperimetry test to standardize any learning effect.

PDT used half the normal dose of verteporfin (Visudyne, Novartis AG, Bülach, Switzerland); that is, 3 mg/m^2 infusion of verteporfin. Verteporfin was infused over 8 minutes, followed by laser 10 minutes from the commencement of infusion. A total light energy of 50 J/cm^2 for 83 seconds was delivered to the area of choroidal hyperperfusion as observed in indocyanine green angiography. In all cases this area was within the central 20 degrees. After treatment, protective spectacles were given, and patients were instructed to avoid strong light for 2 days. The patients had further microperimetry tests, as part of follow-up, 1, 3, and 6 months after treatment. The patient's subjective feelings after treatment were sought at each follow-up examination.

The repeated ANOVA and Bonferroni post hoc test were used to assess improvement in function after treatment. Mann-Whitney *U* test was used to assess differences between groups. SPSS for Windows, version 15.0 (SPSS Inc, Chicago, Illinois, USA), was used for the statistical analysis. $P < .05$ was considered statistically significant.

RESULTS

TWENTY-FOUR EYES FROM 24 CASES OF CHRONIC CSC WERE included in this series. Patients were 21 men and 3 women, whose ages ranged from 34 to 55 years (mean, 46 years). Pretreatment BCVA range was 20/25 to 20/200. All eyes had had 1 or more previous CSC episodes, and the mean duration of the current episode was 4 to 6 months. Before treatment all patients had SRF on OCT examination. Before treatment 10 of 22 eyes (45%) had bilateral involvement on fluorescein angiography, with some RPE

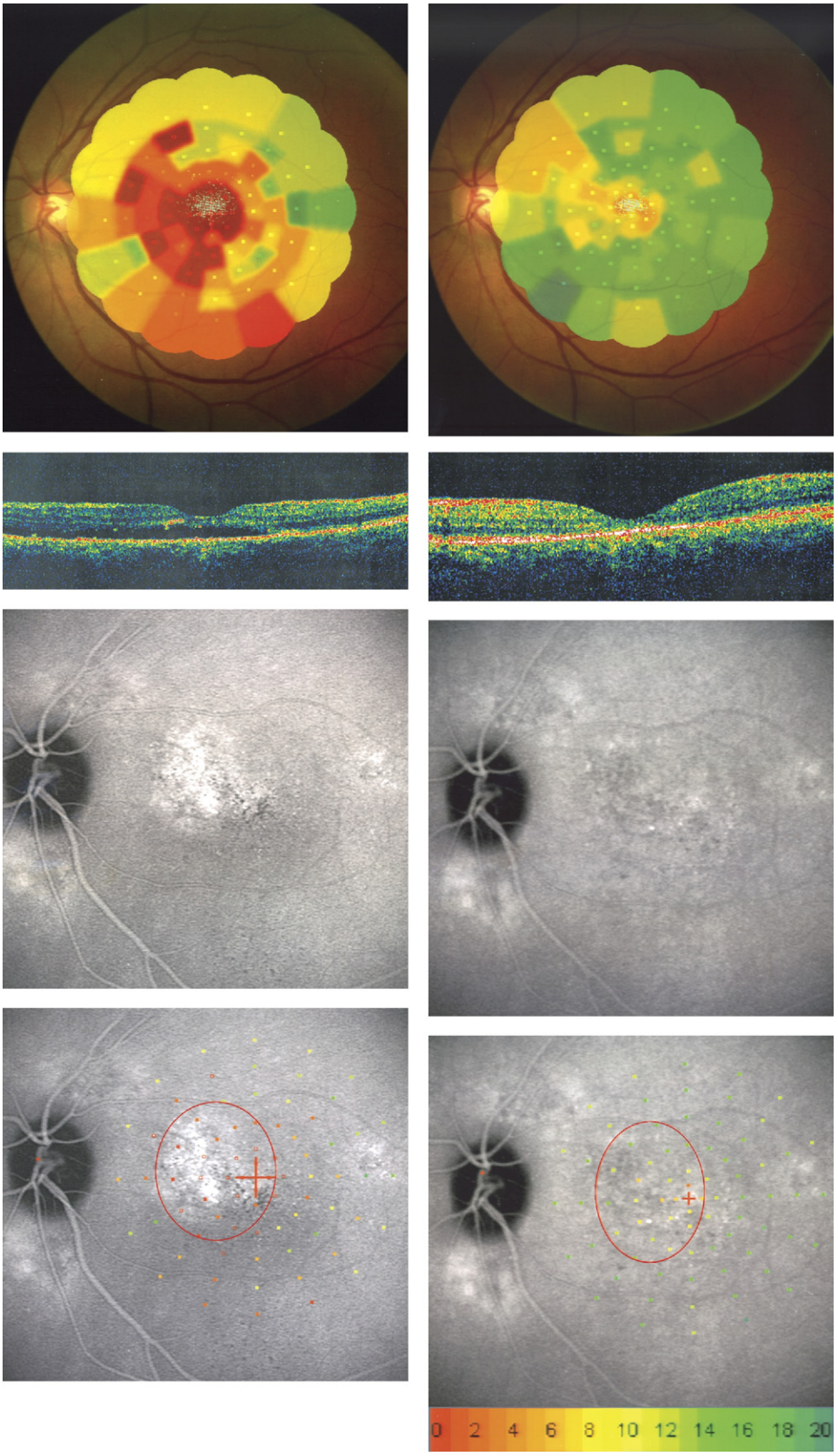

FIGURE 1. Left eye of a 45-year old man with central serous chorioretinopathy (CSC) (Patient 9). (Top left) MP-1 image at the first examination shows that reduced retinal sensitivity points are concentrated in the retinal area. (Top right) MP-1 color mapping

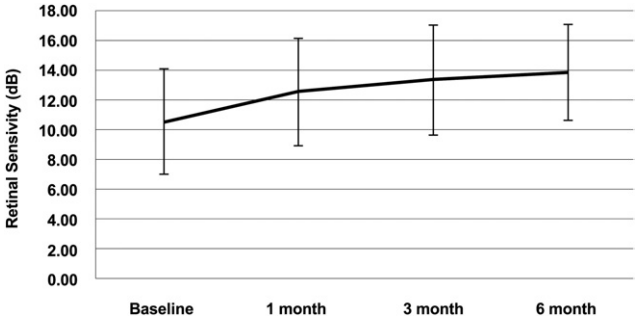

FIGURE 2. Graph showing the serial changes in microperimetry mean retinal sensitivity in the central 20 degrees in cases of central serous chorioretinopathy after half-dose verteporfin photodynamic therapy. Error bars show the standard deviation of the mean.

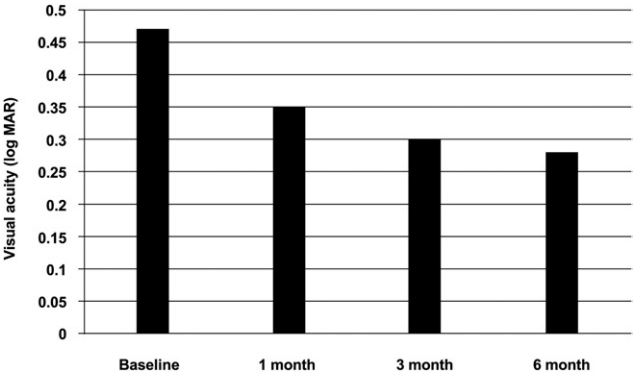

FIGURE 3. Graph showing the serial changes in the mean logarithm of the minimal angle of resolution (log MAR) best-corrected visual acuity in cases of central serous chorioretinopathy after half-dose verteporfin photodynamic therapy.

changes and window defects in the other eye. All patients had subjective improvement of symptoms. The PDT was applied within the central 20-degree area in all patients. The mean spot size was 2500 ± 455 μm (range 1700-3300 μm). The clinical characteristics of eyes with CSC at baseline and 1, 3, and 6 months after treatment are reported in Table 1.

Compared with pretreatment BCVA (log MAR) (0.47 ± 0.28), the mean post-treatment BCVA improved significantly (0.35 ± 0.32 at 1 month [$P < .001$], 0.30 ± 0.34 at 3 months [$P < .001$], and 0.28 ± 0.31 at 6 months [$P < .001$]). As measured with microperimetry, mean retinal sensitivities within the central 10-degree, 20-degree, and paracentral 10-degree to 20-degree fields, which were 8.17 ± 4.31, 10.52 ± 3.53, and 11.79 ± 3.33 dB at baseline, improved to 11.08 ± 4.61 ($P < .001$), 12.55 ± 3.56 ($P < .001$), and 13.51 ± 3.47 dB ($P < .001$) at 1 month, and to 12.45 ± 4.32 ($P < .001$), 13.28 ± 3.71 ($P < .001$), and 13.74 ± 3.75 dB ($P < .001$) at 3 months and to 12.95 ± 3.90 ($P < .001$), 13.74 ± 3.21 ($P < .001$), and 14.22 ± 3.41 dB ($P < .001$) at 6 months.

The mean microperimetric numbers of measurement points in PDT area were 14.5 ± 3.6 (range 9 to 22 locations). Compared with pretreatment mean retinal sensitivity over the PDT area, 7.41 ± 4.29 dB, the post-treatment mean retinal sensitivity over the PDT area improved significantly (10.39 ± 4.45 dB at 1 month [$P < .001$], 11.72 ± 4.53 dB at 3 months [$P < .001$], and 12.23 ± 4.07 dB at 6 months [$P < .001$]) (Table 2).

By the first month after treatment, 20 of 24 eyes (83%) showed complete resolution of SRF. At 3 and 6 months after treatment, SRF had resolved in the remaining 4 eyes (17%) (Cases 4, 8, 12, and 13). There were no statistical differences in baseline retinal sensitivity and retinal sensitivity 1, 3, and 6 months after treatment between eyes with SRF that resolved at 1 month after treatment (n = 20) and eyes with SRF that resolved at 3 and 6 months after treatment (n = 4). The 4 patients whose fluid resolved at 3 and 6 months were older than those with resolution at 1 month ($P < .001$). No recurrence of SRF was observed. One, 3, and 6 months after half-dose PDT, the mean retinal sensitivity had increased significantly (Tables 1 and 2 and Figures 1 and 2), and the mean BCVA had improved significantly (Table 1 and Figure 3). In 6 eyes BCVA did not change, but MP-1 sensitivity increased after treatment. Even with unchanged BCVA in those cases, there was subjective improvement (Table 1).

None of the patients developed any systemic adverse events associated with verteporfin treatment, including infusion site complications and lower back pain. None experienced any subjective or objective drop in vision immediately after treatment or by the subsequent follow-up examination. Neither RPE atrophy nor the development of CNV was observed.

image shows improved retinal sensitivity at the examination 6 months after half-dose of verteporfin photodynamic therapy (PDT). Blue data points represent the locations used for fixation during microperimetric testing. (Second row left) Baseline optical coherence tomography (OCT) shows a layer of thick subretinal fluid. (Second row right) OCT at 6 months shows complete resolution of the subretinal fluid. (Third row left) Baseline late-phase indocyanine green angiography (ICGA) shows the leakage area. (Third row right) Late-phase ICGA at 6 months shows resolution of the leakage. (Bottom left) To assess microperimetry results over the treated area, we superimposed sensitivity data on the ICGA image of the Heidelberg scanning laser ophthalmoscope at baseline. (Bottom right) Six months after treatment. (Bottom) In this patient, half-dose of vertoporfin PDT was applied with a spot size of 3000 μm (red circle) to cover the choroidal abnormality at macular area. Note that retinal sensitivity was improved in spot area (red circle) from 1 dB (baseline) to 10.3 dB at 6 months after treatment.

DISCUSSION

SEVERAL STUDIES HAVE REPORTED A FAVORABLE OUTcome when using PDT for treating chronic CSC.[6–12] This approach is based on the notion that choroidal hyperpermeability, as demonstrated by indocyanine green angiography, is an underlying contributor to SRF accumulation. The presumed therapeutic mechanism of action of PDT in these cases is closure of vascular channels in the choriocapillaris.[6] But there are some safety concerns about the standard dose of PDT. Cardillo Picolino and associates showed secondary RPE changes after PDT that were thought to be the result of hypoxic damage caused by choriocapillaris occlusion.[8] Chan and associates observed the development of juxtafoveal CNV 3 months after PDT with a standard dose of verteporfin for treating chronic CSC.[9] These potential side effects might be important reasons for restricting the extensive use of full-dose PDT for chronic CSC. Studies have shown that cytotoxicity and vascular damage associated with PDT are dosage dependent.[17,18] In order to enhance the efficacy of PDT in treating CSC while minimizing its side effects, it has been suggested that modified PDT protocols, in terms of verteporfin dosage, fluence rate, the time course of delivery, or a combination may be more appropriate.[12,19,20] By using a reduced half-dose of verteporfin, Lai and associates found that 85% of 20 eyes (18 case of chronic CSC) had complete resolution of serous retinal detachment.[12] In another prospective study, by using half-doses of verteporfin, a faster infusion, and a shorter drug-light interval, it was reported that treatment effects were sustained at the 1-year follow-up as a complete resolution in 43 of 48 eyes (90%), without systemic or ocular side effects.[19] Also, the fluence rate can be optimized. Reibaldi and associates recently reported efficacy of low-fluence (25 J/cm^2) compared with standard-fluence (50 J/cm^2) PDT for treating chronic CSC.[20]

In macular diseases, microperimetry allows accurate analysis of central retinal sensitivity. During measurement, the autotracking function corrects shifts in the measurement position from small, involuntary movements, thereby allowing accurate measurement of the central visual field even in cases of unstable fixation. Microperimetric changes after PDT in different disorders have been extensively studied. For example, Schmidt-Erfurth and associates showed preservation of the central visual field after PDT in patients with subfoveal CNV associated with age-related macular degeneration.[15] In another report, the effect of PDT on macular function of patients with myopic CNV was evaluated with MP-1 microperimetry.[21] Unfortunately, limited information is available on retinal sensitivity after PDT for CSC. Reibaldi and associates described anatomic and functional outcomes in 2 cases of long-standing severe chronic CSC treated with low-fluency PDT. They treated patients with PDT guided by indocyanine green angiography with a fluence of 25 J/cm^2 at an irradiance of 300 mW. At 1 and 9 months after PDT, they observed complete resolution of SRF and improvement of sensitivity in both cases.[22]

In the current study, the mean retinal sensitivities within the central 20-degree field were increased from baseline after treatment in all patients. Our results also showed that eyes with CSC had significantly better retinal sensitivity from baseline after treatment in both the central and paracentral area. This means that the annular area between 10 degrees and 20 degrees also had increased retinal sensitivity after treatment. There were 6 eyes whose BCVA did not change, but retinal sensitivity increased after treatment. Retinal sensitivity in the macular area improved after half-dose PDT, which may explain the concurrent improvement of subjective central vision. The results for increase in mean retinal sensitivity by PDT also support the outcomes for distance BCVA of many investigations.[23,24] Another important finding of the present study was that retinal sensitivity in the treated area was improved after treatment. Improved retinal sensitivity of the treated area might be an important indicator of the absence of treatment-induced adverse effects.

Decreased retinal sensitivity may reflect photoreceptor dysfunction attributable to SRF or photoreceptor cell loss itself. When extensive leakage was resolved, which means a decrease in SRF, the area of scotoma was less. In most of the cases, these beneficial effects were obtained as early as 1 month after treatment. In this study, 20 eyes (83%) showed complete resolution of SRF within the first month after the treatment; the remaining 4 eyes showed resolution of SRF at 3 or 6 months after the treatment.

In addition to anatomic restoration and increase in BCVA, half-dose PDT also improved central macular function. Although 6 months of follow-up are insufficient to draw conclusions on any treatment, use of MP-1 microperimetry enabled us to evaluate accurately the retinal sensitivity and scotoma size in eyes with CSC that had received PDT. In addition to BCVA, measurement of retinal sensitivity would be a help in evaluation of the effectiveness of half-dose PDT in eyes with CSC. Because this uncontrolled study consisted of a small number of patients, with a short follow-up period, further prospective studies with control groups are necessary to determine the effectiveness of PDT on the retinal sensitivity.

THE AUTHORS INDICATE NO FINANCIAL SUPPORT OR FINANCIAL CONFLICT OF INTEREST. INVOLVED IN DESIGN OF STUDY (F.S., M.K., H.O., S.A.K., O.U.); conduct of study (F.S., M.K., H.O., S.A.K.); collection of data (F.S., M.K., H.O., S.A.K.); management (F.S., M.K., H.O., S.A.K.); analysis and interpretation of data (F.S., M.K., H.O., S.A.K., O.U.); and preparation (F.S., M.K., H.O., S.A.K.), review (F.S., M.K., H.O., S.A.K.), and approval of the manuscript (F.S., M.K., H.O., S.A.K., O.U.). The current study was approved by the Institutional Review Board of the Alman Hospital, Taksim, Istanbul, Turkey, and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each patient.

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Biosketch

Fevzi Senturk, MD, graduated from Osmangazi University School of Medicine and completed his fellowship in retina, macula and vitreus disease and surgery in Istanbul Retina Institute, where he continues his work.