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ORIGINAL PAPER

Efficacy of reduced-fluence photodynamic therapy for central serous chorioretinopathy associated with combined serous retinal detachment and fovea-involving pigment epithelial detachment

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Abstract The purpose of the study was to evaluate the effect of reduced-fluence photodynamic therapy (RFPDT) for chronic central serous chorioretinopathy (CSC) associated with serous retinal detachment (SRD) and fovea-involving pigment epithelial detachment (PED). Ten eyes of ten patients with chronic CSC associated with combined SRD and PED involving the fovea were included. RFPDT was applied to the hyperfluorescent area identified at the mid-to-late phase of indocyanine green angiography, which indicated the area of leakage. We evaluated the changes in best-corrected visual acuity (BCVA) and optical coherence tomography at month 1 and final follow-up visit. The mean age of the participants was 47.4 ± 7 years. The mean follow-up duration was 6.3 ± 4 months. At month 3, the SRD had resolved completely in all ten eyes (100 %), and PED had resolved in seven eyes (70 %). The initial mean BCVA improved from 20/50 at baseline to 20/32 at the last visit ($P > 0.05$). The mean central retinal thickness was reduced from 534 ± 279 μm at baseline to 194 ± 46 μm at the last examination ($P < 0.001$). The mean subfoveal choroidal thickness decreased from 461 ± 57 at baseline to 369 ± 75 at the final visit ($P < 0.001$). Reduced-fluence PDT appears as an effective treatment for chronic CSC cases associated with SRD and fovea-involving PED.

Keywords Central serous chorioretinopathy · Fovea-involving pigment epithelial detachment · Indocyanine green angiography · Optical coherence tomography · Reduced-fluence photodynamic therapy · Serous retinal detachment

Introduction

Central serous chorioretinopathy (CSC) is an idiopathic disease characterized by serous retinal detachment (SRD) and/or pigment epithelial detachment (PED) at the posterior pole. Despite advances in imaging modalities and numerous studies, the pathophysiology of CSC is not completely understood. Increased permeability of the choroidal vessels, which is shown by indocyanine green angiography (ICGA), seems to be the mechanism of fluid accumulation between the layers [1]. Hyperpermeable choroidal vessels are thought to increase tissue hydrostatic pressure which promotes the formation of PED, by overwhelming the barrier function of the retinal pigment epithelium (RPE) and leading to fluid accumulation between the retina and RPE [2]. In most cases, CSC is self-limiting and the visual prognosis usually good. However, in chronic CSC cases with persistent SRD and PED, progressive visual loss may

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develop due to cystoid edema of the neurosensory retina or decompensation of the RPE [3, 4].

Photodynamic therapy (PDT) using verteporfin for CSC with subfoveal leakage has been reported to be safe and effective in reducing subretinal fluid (SRF) and increasing visual acuity (VA) in most patients [5–8]. The PDT protocol using half dose of verteporfin to treat CSC was reported to be as effective as conventional PDT and also minimized the deleterious effect on choriocapillaris perfusion [9–12]. Safety-enhanced PDT with half-dose verteporfin does not lead to significant reduction of central retinal thickness in eyes with PED associated with chronic CSC [10].

The presence of PED at the baseline optical coherence tomography (OCT) examination has been proposed as prognostic factor for incomplete resolution of serous macular detachment and worse visual outcomes after treatment with PDT with half-dose verteporfin [13]. On the basis of these findings, it has been speculated that PDT using half-dose verteporfin is more effective for treating chronic CSC without PED [10, 13]. Very few reports have addressed treatment methods and outcomes for chronic CSC with fovea-involving PED. Therefore, we tried to estimate the efficacy of reduced-fluence PDT (RFPDT) for chronic CSC associated with combined SRD and PED involving the fovea.

Materials and methods

Study design and patient recruitment

We retrospectively reviewed the medical records of 148 patients who had received PDT with verteporfin for the treatment of CSC at the Istanbul Retina Institute from January 2005 to September 2015. Ten patients (ten eyes) with a diagnosis of chronic CSC associated with combined SRD and PED involving the fovea were included in the study. Written informed consent was obtained prior to the diagnostic and therapeutic procedures. The study protocol was approved by the Institutional Review Board of Sisli Memorial Hospital, Istanbul. The study adhered to the tenets of the Declaration of Helsinki.

The inclusion criteria were as follows: (1) a history of vision loss for at least 3 months; (2) persistence of SRD and PED involving the fovea for at least 3 months, documented with OCT; (3) presence of active angiographic leakage caused by CSC, shown on fluorescein angiography (FA); (4) abnormal dilated choroidal vasculature and other features consistent with the diagnosis of CSC, shown on ICGA; (5) no evidence of choroidal neovascularization (CNV) or polypoidal choroidal vasculopathy on FA or ICGA; (6) no previous PDT treatment. Only the eyes which fulfilled the inclusion criteria were included.

Photodynamic therapy

All patients received an infusion of verteporfin (Visudyne; Novartis, Basel, Switzerland) of 6 mg/m^2 body surface area over 10 min followed by laser delivery at 689 nm 5 min after the start of the infusion. Using the Opal Photoactivator (Coherent Inc, Santa Clara, California, USA) and standard light intensity of 600 mW/cm^2, the irradiation time was shortened to 41s.The area of irradiation was set to cover the hyperfluorescent area of the leakage shown during the mid-to-late phase of ICGA and the fovea-involving PED. After treatment, protective spectacles were given, and patients were instructed to avoid direct sunlight for 2 days.

Baseline and follow-up examinations

All participants underwent comprehensive ophthalmic examinations including BCVA according to ETDRS (Early Treatment Diabetic Retinopathy Study) charts, refraction, slit-lamp biomicroscopy, tonometry, and dilated fundus examination with a 90-diopter lens. Following the fundus photography (Carl Zeiss, Inc., Jena, Germany), the Spectralis OCT system (Heidelberg Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany) was used for fundus autofluorescence, macular scans, choroidal imaging, digital FA, and ICGA. Digital FA and ICG angiography were performed at baseline. Best-corrected visual acuity (BCVA), fundus observations, and OCT measurements to document the presence of subretinal fluid as well as pigment epithelial detachment were obtained at baseline and after PDT at month 1, month 3, and final visit.

We evaluated the changes in central retinal thickness, PED, subfoveal choroidal thickness, and BCVA before and after the RFPDT. We measured central retinal thickness from the outer surface of the neurosensory retina to the inner surface of RPE. The

height of the PED was defined as the distance between the upper surface of the detached RPE and the inner surface of the choroid. The subfoveal choroidal thickness was measured from the inner surface of the choroid to the inner surface of the sclera. At least two measurements were performed by two experienced ophthalmologists blinded to the study protocol and averaged.

Data analysis

The BCVA was converted to logMAR (logarithm of the minimal angle of resolution) for the analysis. We compared the BCVA and anatomical changes before and after RFPDT, using the Friedman test and post hoc Dunn's test. Spearman's rank correlation was used to test the correlation between the height and diameter of the PED. The Wilcoxon signed-rank test was used to compare the baseline choroidal thickness between the affected and the fellow eye. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS), version 19.0, by IBM.

Results

Demographics, baseline clinical features, and visual acuity

The demographic characteristics, baseline clinical findings, and BCVA are summarized in Table 1. The mean age of the patients was 47.4 ± 7 years (range, 31–54 years). Seven patients were male (70 %) and 3 were female (30 %). The mean logMAR BCVA at presentation was 0.37 ± 0.3 (range, 1.0–0.1), equivalent to the Snellen BCVA of 20/50 (range, 20/200–20/25). The mean spherical equivalent refractive error was 0.83 ± 2 diopters. Three of the eyes (30 %) had one or more previous episodes of CSC, and the mean duration of the current episode was 7.8 ± 6 months (range, 3–18 months). Three eyes (30 %) had been treated in another clinic with bevacizumab previously and showed no obvious changes (Case 2, 3 and 7). In two of the fellow eyes, PED without symptoms was observed in the area nasal and inferior to the fovea. In one fellow eye, PED including the fovea with symptoms of distortion and blurred central vision was detected. One patient had significant vision loss in the fellow eye because of macular atrophy associated with chronic CSC. The mean laser spot size was 4140 ± 1135 μm (range, 2500–5500 μm), and the mean follow-up duration after PDT was 6.3 ± 4 months (range, 3–12 months). At baseline, all ten eyes showed hyperfluorescence on mid- and late-phase ICGA and hypofluorescence related to the subretinal fluid. Baseline FA showed hyperfluorescent leakage in all eyes, with hypofluorescent subretinal fluid and late-phase hyperfluorescence related to the PED in five eyes.

Visual acuity changes after reduced-fluence photodynamic therapy

The changes in VA after RFPDT are shown in Table 1. At the first month after the RFPDT session, the mean logMAR BCVA improved from 0.37 ± 0.3 (Snellen equivalent 20/50) to 0.23 ± 0.2 (Snellen equivalent 20/32). The BCVA remained stable during posttreatment follow-up, with a mean final VA of 0.25 ± 0.3 logMAR (Snellen equivalent: 20/32). Although the Friedman test showed that these results are statistically significant ($P = 0.004$), the post hoc Dunn's test failed to detect any significant difference between the mean baseline and posttreatment VA ($P < 0.05$). Seven eyes had improved vision at the last examination, with a mean 2.4 Snellen lines gained; two eyes had stable vision; and one eye had worse vision at the final visit.

Baseline optical coherence tomography parameters and anatomical changes after reduced-fluence photodynamic therapy

Baseline OCT parameters and anatomic changes after RFPDT are summarized in Table 2. The mean baseline central retinal thickness was 534 ± 279 μm (range, 237–965 μm). The mean baseline central retinal thickness of the fellow eye was 224 ± 40 μm (range, 171–312 μm). At baseline, the mean height and diameter of PED including the fovea were 294 ± 178 μm (range, 101–579 μm) and 1074 ± 366 μm (range, 712–1678 μm), respectively (Fig. 1). The height and the diameter of PED showed significant correlation (Spearman's rho, $r = 0.75$, $P < 0.01$). The mean baseline subfoveal choroidal thickness was 461 ± 57 μm (range, 381–550 μm). It was

Table 1 Demographic data and baseline, and posttreatment best-corrected visual acuity of eyes with combined serous retinal detachment and fovea-involving pigment epithelial detachment

Case	Age (years)	Eye	Sex	Symptom duration (months)	BCVA (Snellen equivalent)			PDT spot size (μm)	Follow-up (months)
					Baseline	1 Month	Last follow-up		
1	46	OD	M	17	20/100	20/32	20/32	5500	3
2	31	OD	M	3	20/50	20/32	20/32	5500	6
3	51	OD	M	3	20/200	20/200	20/200	4000	3
4	53	OS	F	3	20/32	20/25	20/25	3200	3
5	53	OD	F	6	20/25	20/25	20/20	3500	12
6	53	OS	M	12	20/32	20/25	20/100	3200	12
7	49	OS	M	10	20/25	20/25	20/25	2500	6
8	37	OD	M	3	20/100	20/32	20/25	5000	3
9	47	OS	F	3	20/25	20/25	20/20	3500	12
10	54	OD	M	18	20/32	20/32	20/25	5500	3

BCVA best-corrected visual acuity, *PDT* photodynamic therapy

Table 2 Baseline optical coherence tomography parameters and anatomic changes after reduced-fluence photodynamic therapy

Case	Baseline PED (μm)		Central retinal thickness (μm)				Subfoveal choroidal thickness (μm)			
	Height	Diameter	Baseline	Baseline fellow eye	1 Month	Last follow-up	Baseline	Baseline fellow eye	1 Month	Last follow-up
1	574	1283	600	204	178	161	488	439	345	339
2	390	1170	965	254	170	198	550	571	511	499
3	145	542	212	196	187	182	509	470	402	470
4	173	882	307	221	209	201	413	401	343	361
5	579	1517	750	219	255	178	511	368	393	370
6	262	1204	469	195	222	270	445	415	364	380
7	377	1678	631	252	245	256	391	381	391	361
8	189	712	904	312	150	184	496	403	447	380
9	134	1024	263	219	174	202	381	351	305	263
10	101	723	237	171	122	106	430	286	315	260

PED pigment epithelial detachment

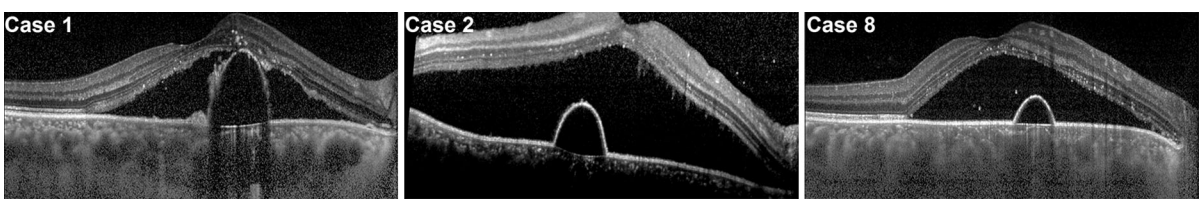

Fig. 1 Baseline optical coherence tomography images of combined serous retinal detachment and fovea-involving pigment epithelial detachment treated with reduced-fluence photodynamic therapy (*Cases* 1, 2, and 8 from *left* to *right*)

significantly thicker than that of the fellow eye (409 ± 76 μm, range 286–571 μm; Wilcoxon's signed-rank test, $P < 0.01$).

The mean central foveal thickness decreased from 534 ± 279 μm at baseline to 191 ± 41 μm at 1 month (range, 122–255 μm, post hoc Dunn's test,

$P < 0.001$) and 194 ± 46 μm at the final visit (range, 106–270 μm, post hoc Dunn's test, $P < 0.001$). The mean subfoveal choroidal thickness decreased from 461 ± 57 μm to 382 ± 62 μm at month 1 and 369 ± 75 μm at the final visit (post hoc Dunn's test, $P < 0.001$). One month after the application of RFPDT, the PED and SRF had resolved completely in five eyes (50 %). Two eyes (20 %) had SRD, two eyes (20 %) had PED, and one eye (10 %) had a combination of SRD and PED. Three months after the treatment, complete resolution of SRF was observed in all eyes. In three eyes (Case 2, 3 and 6), the PED had decreased in height, but did not show complete regression until the last visit (Fig. 2, Case 2). Among the three eyes with PED at 3 months, one (case 6) received a second session of RFPDT at 6 months due to recurrence of SRD and persistence of PED. In this patient, the SRF resolved 1 month after the second RFPDT application; however, the PED persisted until the last follow-up visit at 12 months.

None of the patients developed any systemic adverse event associated with verteporfin infusion. None had any visual loss immediately after RFPDT. Complications of PDT such as CNV and RPE tear during the follow-up period were not observed.

Discussion

We found that RFPDT was effective for resolving combined SRD and PED including the fovea in eyes with chronic CSC. After a mean follow-up of 6 months, SRF resolved completely in all ten eyes. Seven eyes showed dramatic resolution of fovea-involving PED 1 month after PDT, but in three eyes, although decreased, the PED persisted until the last visit. Among the three eyes with PED at 3 months, one received a second session of PDT at 6 months due to recurrence of SRF and persistence of serous PED.

Especially in chronic CSC, prolonged detachment of the macula leads to RPE atrophy and neurosensory retinal changes that result in permanent loss of visual function, including visual acuity, color vision, and contrast sensitivity [14]. The aims of the treatment of CSC are to induce reattachment of the neurosensory retina and RPE, to improve or preserve visual acuity, and to prevent recurrences. Photodynamic therapy with verteporfin has been shown as a promising effective treatment. The ICGA finding of mid-phase hyperfluorescent choroidal plaques consistent with choroidal hyperpermeability suggests that treatment targeted at the choroidal vasculature might address the exact cause of the disease. In some studies, CSC with PED including the fovea has been associated with a poorer visual prognosis [4, 13, 15].

Mudvari et al. [15] reported that, during a mean follow-up period of 49 months, PED associated with CSC disappeared spontaneously in 65 % of cases, and mean visual acuity improved. However, they also reported that visual acuity declined in 50 % of their patients who had PED at the fovea.

Lai et al. [10] evaluated the short-term safety of an enhanced PDT protocol with half-dose verteporfin for treating chronic CSC in 20 eyes. At baseline, seven eyes had both SRD and PED on OCT examination. Subgroup analysis showed that the reduction in central retinal thickness and improvement in BCVA for eyes with PED was not statistically significant. In a retrospective multicenter study with follow-up from 1 month to more than 1 year, Lim et al. [16] aimed to create a database of cases of CSC treated with PDT. Fifty-six eyes (21 %) had combined SRD and PED, and 17 eyes (7 %) had PED. They reported that 65 % of PEDs resolved after PDT.

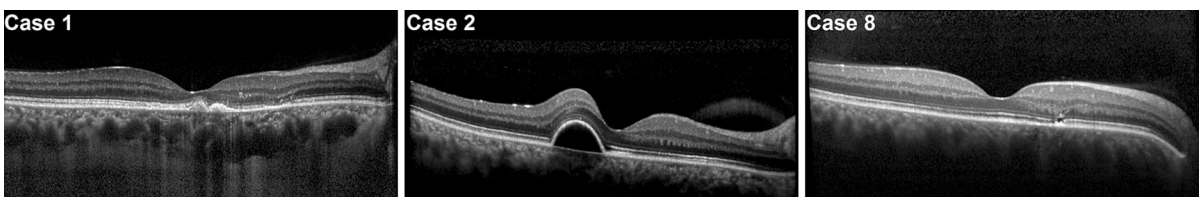

Fig. 2 Optical coherence tomography images from the cases in Fig. 1 at final visit after reduced-fluence photodynamic therapy (*Cases* 1, 2, and 8 from *left* to *right*). The pigment epithelial detachment in *Case* 2 persisted until the last visit at 6 months. The serous retinal detachment and pigment epithelial detachment in *Cases* 1 and 8 had resolved at the last visit

Chan et al. [13] have evaluated the efficacy of safety-enhanced PDT for treating chronic CSC. In a prospective study including 40 eyes, 6 eyes had combined SRD and PED, and 7 eyes had isolated PED involving the fovea. Nine of the 13 eyes with combined SRD and PED or isolated PED at baseline had complete resolution at 12 months. Among the 4 eyes with persistent serous maculopathy at 12 months, 2 had isolated serous PED and 2 had combined SRD and PED. According to the results of the study, the presence of PED at baseline OCT was proposed as a prognostic factor for incomplete resolution of serous macular detachment and an important prognostic factor for worse visual outcomes after PDT treatment with half-dose verteporfin. Chan et al. [13] speculated that PDT with half-dose verteporfin might be more effective in treating chronic CSC without PED and proposed that the reasons for the poorer response with PED are likely to be multifactorial and may include differences in pharmacokinetics, more severe preexisting RPE damage, less effective laser penetration, and higher PDT toxicity at the RPE layer. Occult choroidal neovascularization with pigment epithelial detachment in age-related macular degeneration similarly had poorer response to PDT treatment [17].

In the present study, the anatomical effects of RFPDT for chronic CSC correspond with the results of previous reports by Chan et al. [13] and Lim et al. [16]. Owing to the limited number of patients included in this study and relatively good baseline VA, the improvement of mean BCVA after RFPDT was not statistically significant, consistent with the results of Lai et al. [10]. In contrast, the reduction of central retinal thickness observed in our study population was significant.

On the other hand, Ruiz-Moreno et al. [18] evaluated the efficacy of conventional PDT for chronic CSC in a retrospective multicenter study of 82 eyes. Four cases presented with serous PED prior to the therapy. Final BCVAs in these cases were above the average for the whole group. Although the size of this subgroup was small, these data suggest that PED is not an indicator of worse visual prognosis.

Goto et al. [19], in a retrospective study, postulated that serous PED accompanying hyperfluorescence on ICGA is considered as a variant of CSC and performed reduced-fluence PDT (RFPDT) to treat foveal PED in 15 eyes. The PED had completely resolved 1 month after RFPDT in 93 % of cases, and recurrence was not observed during 3 months of posttreatment follow-up. The follow-up period after RFPDT treatment reported by Goto et al. [19] was short (3 months). On the other hand, Shinojima et al. [20] reported recurrence of PED within 1 year of treatment with half-dose verteporfin in 31 % of eyes with chronic CSC that initially had reattachment of the PED at 6 months. Five patients in our study population were followed up for 3 months, and 5 were followed up from 6 months to 1 year. We observed no recurrence in PED during a mean follow-up of 6 months. However, in 3 of the eyes, the fovea-involving PED showed resistance to RFPDT and remained until the last visit. One of the patients with persistent PED showed recurrence of SRF at 6 months and was treated with a second RFPDT procedure.

Moon et al. [21] investigated the effects and prognostic factors related to PDT for CSC. The presence of fovea-involving PED was associated with increased risk of foveal atrophy and visual loss of more than three Snellen lines. Although not statistically significant, we observed an improvement in BCVA after RFPDT in our study population. A decrease in BCVA associated with foveal atrophy was observed in only one eye after 12 months of follow-up.

This study is limited by its retrospective nature, relatively small sample size, and short follow-up period. In spite of these limitations, our study suggests that RFPDT with verteporfin induces a rapid resolution of macular SRD and fovea-involving PED, which is followed by improvement and/or preservation of vision. The anatomical and functional results of RFPDT application for chronic CSC associated with combined SRD and PED involving the fovea appear promising. These results emphasize the role of choroidal vascular permeability on the pathogenesis of CSC and the effectiveness of RFPDT for this condition. Extensive prospective, randomized, controlled trials would establish the most effective and safest PDT protocol for the treatment of chronic CSC associated with fovea-involving PED.

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Compliance with ethical standard

Conflict of interest The authors declare that they have no conflict of interest.

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