Focal and Diffuse Chronic Central Serous Chorioretinopathy Treated With Half-Dose Photodynamic Therapy or Subthreshold Micropulse Laser: PLACE Trial Report No. 3

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• PURPOSE: To compare the outcome between high-density subthreshold micropulse laser (HSML) treatment and half-dose photodynamic therapy (PDT) in chronic central serous chorioretinopathy (cCSC) patients, subdivided based on either focal or diffuse leakage on fluorescein angiography (FA).

• DESIGN: Retrospective analysis of multicenter randomized controlled trial data.

• METHODS: Patients were treated with either half-dose PDT or HSML (both indocyanine green angiography–guided) and categorized in 2 groups, based on focal or diffuse leakage on FA. Clinical outcomes were evaluated at baseline and during follow-up.

• RESULTS: In the focal leakage group (63 patients), both at first evaluation and at final visit, more PDT-treated than HSML-treated patients demonstrated a resolution of subretinal fluid (evaluation visit 1: 57% in the PDT group and 17% in the HSML group, $P = .007$; final visit: 75% and 38%, $P = .012$). In the diffuse leakage group (93 patients), both at first evaluation and at final visit, more PDT-treated than HSML-treated patients showed a resolution of subretinal fluid (evaluation visit: 1:48% in the PDT group and 16% in the HSML group, $P = .002$; final visit: 67% and 21%, $P = .002$). PDT-treated patients in the focal and diffuse leakage group had a higher retinal sensitivity increase, comparing baseline and final visit ($+3.1 \pm 3.1$ dB vs $+1.2 \pm 4.0$ dB, $P = .048$, and $+2.7 \pm 3.3$ dB vs $+1.0 \pm 3.8$ dB, $P = .036$, respectively). Only in the diffuse leakage group, the increase in ETDRS letters was higher in the PDT-treated group when comparing baseline and first evaluation visit ($+4.4 \pm 6.1$ vs $+0.9 \pm 10.0$, $P = .049$).

• CONCLUSIONS: Half-dose PDT is superior to HSML treatment in cCSC patients, regardless of the presence of focal or diffuse leakage on FA. (Am J Ophthalmol 2019;205:1–10. © 2019 Elsevier Inc. All rights reserved.)

CENTRAL SEROUS CHORIORETINOPATHY (CSC) IS characterized by an accumulation of subretinal fluid (SRF). The exact pathophysiology has not been elucidated, but it is thought to be a dysfunction of the choroid and/or retinal pigment epithelium (RPE).[1–3] A hyperpermeable and thickened choroid (pachychoroid) may lead to leakage of fluid from the choriocapillaris to the subretinal space, which seems to be paramount in the pathophysiology of CSC.[4] Disruption of the RPE blood-retina barrier can subsequently lead to accumulation of SRF.[5] The classification of CSC is subject to debate, but CSC is usually subdivided into 2 large subgroups: acute and chronic CSC (cCSC). While the acute variant of CSC usually resolves within months with little permanent damage to vision, cCSC can lead to clinically significant irreversible vision loss and reduced quality of life.[6–8] The main treatment options currently in usage for cCSC are photodynamic therapy (PDT), high-density subthreshold micropulse laser (HSML) treatment, and treatment with mineralocorticoid antagonists such as eplerenone.[9–18] Treatment in CSC should aim to achieve a complete and durable resolution of SRF.[19–21] The PLACE trial, the first large prospective multicenter randomized controlled treatment trial in cCSC, showed that half-dose PDT is more effective than HSML, in terms of both anatomic and functional outcome measures.[19] PDT presumably causes a transient ischemia and remodeling of the choriocapillaris, with a reduction in choroidal thickness, leading to a decrease in choroidal hyperpermeability and

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consequently reduced SRF leakage.[22,23] The mechanism of action of HSML treatment is unclear, but presumably works through a modulation of retinal and RPE function by delivering energy to the RPE, while preventing denaturation of proteins and other structural damage associated with conventional continuous pulse laser treatment.[16,24] It has been postulated that HSML treatment may be unsuitable for patients with diffuse leakage and diffuse RPE decompensation.[2,25] Patients affected with cCSC can be further categorized into subgroups, based on abnormalities on multimodal imaging such as the presence of a single focal spot of leakage, or more multifocal diffuse leakage on fluorescein angiography (FA).[26] In PLACE trial report No. 2, no marked clinical differences were found between untreated cCSC patients with focal or diffuse leakage on FA.[27] However, this subdivision may be useful for a personalized treatment in cCSC, as patients with focal leakage on FA may respond differently to treatments such as half-dose PDT and HSML treatment as compared with patients with more diffuse, multifocal leakage. The aim of this study was to analyze whether there are differences in efficacy of half-dose PDT and HSML treatment for focal, localized cCSC vs multifocal, more extensive diffuse cCSC, based on the leakage pattern on FA.

METHODS

IN THIS STUDY, WE ANALYZED PATIENTS WHO WERE PREVIously included in the half-dose Photodynamic therapy versus high-density subthreshold micropulse LAser treatment in patients with chronic CEntral serous chorioretinopathy (PLACE) trial (ClinicalTrials.gov identifier: NCT01797861).[19,28] This randomized controlled trial was performed in 5 academic medical centers located in Cologne (Germany), Oxford (United Kingdom), Leiden and Nijmegen (the Netherlands), and Paris (France). Permission was obtained from the Medical Ethics Committee located in Nijmegen, the Netherlands (number: P13.241). Local Medical Ethical Committees gave permission before start of the trial. This study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all study subjects.

Patients with active cCSC, 18 years of age or older, and with visual loss or presence of SRF for more than 6 weeks up to 18 months were included from November 2013 to September 2016. A diagnosis of active cCSC was confirmed with foveal SRF on spectral-domain optical coherence tomography (SDOCT), a minimum of 1 hyperfluorescent area ("hot spot") of leakage on FA with RPE window defects typical for cCSC, and corresponding hyperfluorescent areas on indocyanine green angiography (ICGA).[28] Exclusion criteria included previous treatment for CSC, current treatment with corticosteroids or such a treatment within the last 3 months before baseline visit, myopia of more than 6 diopters, or evidence of another diagnosis that could explain the accumulation of SRF. Additional exclusion criteria were a best-corrected visual acuity (BCVA) <0.1 (Snellen equivalent), intraretinal fluid, signs of soft drusen or neovascularization, or contraindications to receive either FA or ICGA.

Recruited patients were randomly assigned to receive either half-dose PDT or HSML treatment within 4 weeks after screening visit. First evaluation visit was at 6-8 weeks after treatment, and final visit was at 7-8 months after treatment. Patients were retreated with the same treatment as they were randomized to in the case of persistent SRF at evaluation visit 1. Based on multimodal imaging at screening visit, patients were categorized as having either focal leakage or diffuse leakage, according to a previously described categorization.[29] Patients with focal leakage had a maximum of 1 "hot spot" of leakage on FA. An increase in the area of hyperfluorescence between early- and late-phase FA was considered to be a "hot spot" of leakage. Diffuse leakage on FA was defined as either >1 "hot spot" of leakage or a larger area of hyperfluorescent leakage, not directly linked to 1 point in origin. Good interobserver agreement rates and Cohen's kappa coefficient were obtained from 2 independent graders for this classification (90% and 0.80, respectively).

• **PHOTODYNAMIC THERAPY TREATMENT:** The pupil of the eye to be treated with PDT was dilated with 1.0% tropicamide and 2.5% phenylephrine eye drops, then an intravenous infusion of 3 mg/m^2 (half-dose) verteporfin (Visudyne; Novartis, Basel, Switzerland) was administered within a time frame of 10 minutes. At 15 minutes after the start of infusion, an anesthetic eye drop was administered (oxybuprocaine 0.4% or equivalent) to the eye to be treated, and a PDT lens (Volk, Mentor, Ohio, USA) was positioned on the anesthetized eye. Subsequently, laser therapy with standard fluency of 50 J/cm^2 and a wavelength of 689 nm was applied to the affected area for 83 seconds. The area to be treated was based on hyperfluorescent abnormalities on ICGA, with which the abnormalities on OCT and FA were also taken into account. An example of a PDT treatment protocol is depicted in Figure 1B, as well as in the primary PLACE trial article.[19]

• **HIGH-DENSITY SUBTHRESHOLD MICROPULSE LASER TREATMENT:** The pupil of the eye to be treated with HSML was dilated with 1.0% tropicamide and 2.5% phenylephrine. Then, an anesthetic eye drop was given (oxybuprocaine 0.4% or equivalent), and a contact glass (for instance, a Volk area centralis lens) was positioned on the affected eye. Subsequently, HSML treatment with an 810 nm diode laser with overlapping laser spots was performed on the areas identified on mid-phase ICGA, avoiding a distance of 500 μm or less from the foveal center. A power of 1800 mW, a duty cycle of 5%, frequency of

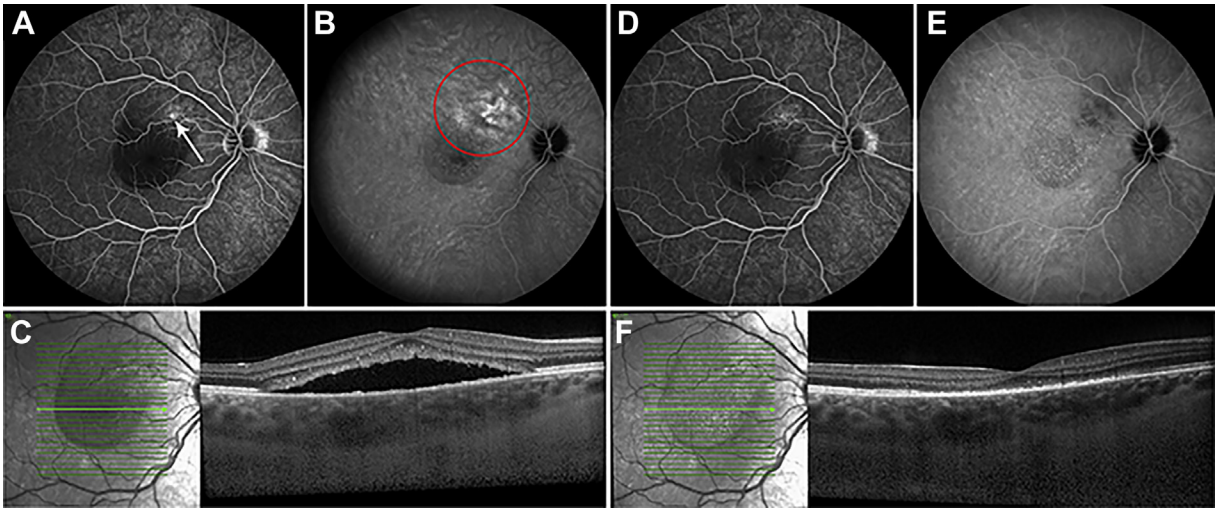

FIGURE 1. Multimodal imaging of a 51-year-old male patient who was diagnosed with chronic central serous chorioretinopathy. (A-C) Imaging prior to treatment with half-dose photodynamic therapy (PDT) is depicted. A "hot spot" of leakage was visible on fluorescein angiography (FA; white arrow; A). The area on indocyanine green angiography (ICGA) that corresponded to the "hot spot" on FA shows intense hyperfluorescence (within the red circle; B). The red circle (B) represents the area that was treated with PDT. Subretinal fluid was present prior to treatment with PDT (C). (D) At the evaluation visit after PDT, the "hot spot" of leakage has resolved and residual diffuse atrophic retinal pigment epithelium alterations were present. (E) On ICGA, hypofluorescence was present at the location of the "hot spot" that had disappeared. (F) The subretinal fluid has completely resolved after PDT treatment.

500 Hz, exposure time of 0.2 seconds per shot, and a spot size of 125 μm were used. The first laser "test" spot was applied just outside the macular area. If retinal discoloration was seen at a power of 1800 mW (corresponding to suprathreshold treatment), the power was reduced with steps of 300 mW until no visible reaction was seen. Multimodal imaging of a cCSC patient treated with HSML is depicted in Figure 2.

• **OUTCOMES:** Clinical characteristics including parameters on multimodal imaging (central foveal thickness [CFT], subfoveal choroidal thickness [SFCT], the size and location of retinal pigment epithelium alterations [RPEA]), retinal sensitivity using microperimetry, and the outcome of a vision-related quality-of-life questionnaire were obtained at each visit. CFT was defined as the distance between the inner limiting membrane and the ellipsoid zone at the location with the maximal foveal dip on SDOCT scan.[20] SFCT was defined as the distance between the RPE and the outer choroid sclera junction on enhanced depth imaging (EDI) OCT. The size of RPEA was categorized as larger or smaller than 5 optic disc diameters. The integrated "draw region" tool in Heidelberg Eye Explorer (Heidelberg Engineering, Heidelberg, Germany) was used when the imaging was ambiguous. The RPEA location was categorized as either foveal or outside the fovea. Retinal sensitivity was obtained with the use of 2 different devices, the MP1 (NIDEK Technologies, Padova, Italy) and the Macular Integrity Assessment (CenterVue, Padova, Italy). During follow-up, microperimetry was performed using the same device for each patient. The retinal sensitivity values were converted using a previously published method.[30] A validated questionnaire (25-item National Eye Institute Visual Function Questionnaire [NEI-VFQ25]) was used to assess vision-related quality of life, which was scored on a scale from 0 to 100.[31]

• **STATISTICS:** Analyses were performed with SPSS Statistics (version 23.0; IBM Corp, Armonk, New York, USA). Independent *t* tests and χ^2 tests were used to assess the differences between the focal and diffuse leakage subgroups within the PDT and HSML treatment groups. *P* values lower than .05 were deemed statistically significant.

RESULTS

BETWEEN NOVEMBER 15, 2013 AND SEPTEMBER 14, 2016, A TOtal of 158 patients (128 male, 30 female) out of 179 patients that were enrolled in the PLACE trial were eligible to be included in this study. Sixteen patients were excluded because the treatment was not performed according to protocol, 3 patients were excluded because they used steroids before evaluation visit 1, and in 2 patients FA was of insufficient quality to categorize them into focal or diffuse leakage. The mean age of the patients at baseline visit was 48.7 ± 8.6 years, and the mean duration of visual symptoms was 7.3 ± 4.4 months. Mean baseline BCVA was 76

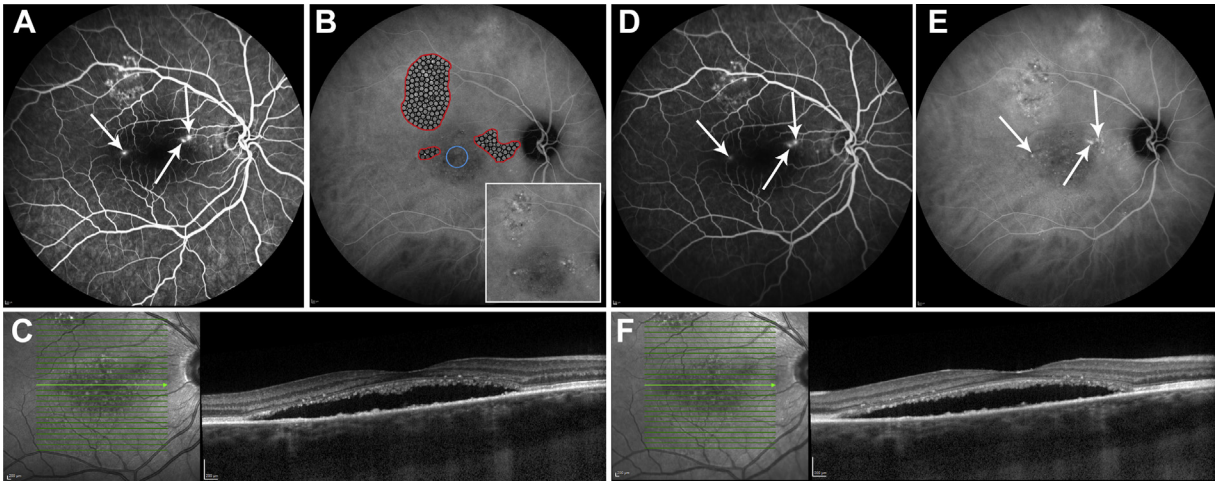

FIGURE 2. Multimodal imaging of a 43-year-old male patient who was diagnosed with chronic central serous chorioretinopathy with multifocal, diffuse leakage. (A-C) Fluorescein angiography (FA; A), indocyanine green angiography (ICGA; B), and optical coherence tomography (OCT; C) before treatment with high-density subthreshold micropulse laser (HSML). The area that was treated with HSML is (schematically) depicted within the border of the red line and included 199 laser spots (B). On FA, multiple "hot spots" of leakage were visible within the foveal area (A; white arrows). Hyperfluorescent abnormalities were visible on ICGA at the same location as the "hot spots" on FA (B). Subretinal fluid was present foveally (C). "Hot spots" of leakage on FA (D; white arrows), hyperfluorescent abnormalities on ICGA (E; white arrows), and subretinal fluid on OCT (F) were still present (D-F; white arrows). HSML treatment was unsuccessful.

± 9 ETDRS letters (Snellen equivalent: 0.7 ± 0.3), mean CFT was 107 ± 26 μm, and mean SFCT was 416 ± 110 μm. Not all patients could be analyzed owing to either direct cross-over to the other treatment arm before final visit, loss to follow-up, the use of intranasal corticosteroids, or the obtained data was of insufficient quality.

• **CHARACTERISTICS OF THE FOCAL AND DIFFUSE LEAKAGE GROUP:** The characteristics of both the focal and diffuse leakage group at baseline show overlap with patients that have been presented in a previous article.[19] The most important baseline characteristics are summarized in Table 1 and multimodal imaging of 2 patients is provided in Figure 1 and Figure 2. No treatment-related side effects have been reported for PDT and HSML treatment.[19] The mean spot size of the patients treated with PDT (which was based on the extent of hyperfluorescent choroidal abnormalities on ICGA) was 3761 ± 1398 μm in the focal leakage group and 4193 ± 1685 μm in the diffuse leakage group ($P = .231$). There were 4 patients in the focal leakage group and 5 patients in the diffuse leakage group in whom the PDT spot did not involve the fovea ($P > .999$). The mean number of spots used for HSML treatment was 113 ± 121 in the focal leakage group and 231 ± 240 in the diffuse leakage group ($P = .015$). The SFCT could be measured in 119 patients (75%) at baseline, in 146 patients (92%) at evaluation visit 1, and in 116 patients (82%) at final visit. At baseline, measurement of the SFCT was not possible owing to insufficient imaging quality in 17 patients (11%), lack of an EDI-OCT scan in 12 patients (8%), and the fact that scleral border was not present within the limits of the OCT scan in 10 patients (6%). There was no significant difference between the focal and diffuse leakage group in the decrease in SFCT between baseline and final visit in the patients treated with HSML (a decrease of 41 μm and 10 μm, respectively, $P = .232$). In the PDT-treated group, there was no significant difference in the decrease in SFCT between baseline and final visit between the focal and diffuse leakage group (60 μm and 78 μm, respectively, $P = .503$). After retreatment with PDT, 11 out of 35 retreated patients (31%) had a complete resolution of SRF, whereas in the HSML treatment group 10 out of 65 patients (15%) had a complete resolution of SRF after a second treatment ($P = .074$).

• **FOCAL LEAKAGE GROUP:** The results of the focal leakage group are presented in Table 2. In the focal leakage group, 30 patients (48%) were treated with HSML treatment and 33 patients (52%) were treated with PDT. The mean age was 47 ± 9 years in the subgroup treated with HSML and 46 ± 9 years in the PDT subgroup ($P = .689$). In the subgroup treated with HSML, the mean duration of symptoms until baseline visit was 6.6 months, whereas the mean duration of symptoms was 8.5 months in the PDT subgroup ($P = .129$). There were 5 patients (16.7%) in the subgroup treated with HSML who had a complete resolution of SRF at evaluation visit 1. These 5 patients had a mean HSML treatment spot number of 93, compared with 117 spots in the patients with persistent SRF ($P = .695$). In the subgroup treated with PDT, there were significantly more patients with resolution

TABLE 1. Baseline Characteristics of Chronic Central Serous Chorioretinopathy Patients With Focal and Diffuse Leakage, Treated With Either Half-Dose Photodynamic Therapy or High-Density Subthreshold Micropulse Laser

	Focal Leakage (N = 63)			Diffuse Leakage (N = 95)		
	HSML (30)	PDT (33)		HSML (49)	PDT (46)	
	Mean	Mean	*P* Value[a]	Mean	Mean	*P* Value[a]
Age at baseline (years)	47 ± 9	46 ± 9	.689	49 ± 8	51 ± 9	.474
Duration symptoms (months)	6.6 ± 4.0	8.5 ± 5.1	.129	7.5 ± 4.4	6.7 ± 4.2	.378
Baseline BCVA (ETDRS letters)	77 ± 8	78 ± 8	.747	75 ± 10	76 ± 9	.586
Baseline BCVA (Snellen)	0.7 ± 0.3	0.7 ± 0.3	.747	0.64 ± 0.3	0.67 ± 0.3	.586
Baseline central foveal thickness (μm)	107 ± 26	107 ± 18	.948	101 ± 25	114 ± 29	.019
Baseline subfoveal choroidal thickness (μm)	431 ± 106	398 ± 117	.505	406 ± 108	428 ± 110	.379
	N (%)	N (%)		N (%)	N (%)	
Sex						
Male	24 (80%)	26 (87%)	>.999	44 (90%)	34 (74%)	.061
Female	6 (20%)	7 (21%)		5 (10%)	12 (26%)	

BCVA = best-corrected visual acuity; ETDRS = Early Treatment of Diabetic Retinopathy Study; HSML = high-density subthreshold micropulse laser; PDT = photodynamic therapy; RPEA = retinal pigment epithelium alterations.

[a]*P* values compared between the PDT- and HSML-treated subgroups.

of SRF at this evaluation visit, 6-8 weeks after treatment (17 patients, 56.7%, $P = .007$). Patients with persistent SRF at evaluation visit 1 received an additional treatment (the same treatment that they were initially randomized to). Out of 39 patients with focal leakage who received a second treatment, 25 received HSML treatment (mean number of treatment spots: 114) and 14 received PDT. After an additional treatment with HSML, 7 patients out of the 25 who received a second HSML treatment (28%) had complete resolution of SRF, as compared with 4 patients (29%) in the second PDT group ($P > .999$). At final visit, 11 out of the 26 patients (41%) with focal leakage who underwent HSML treatment and attended the final visit had a resolution of SRF, and 21 out of the 28 patients (75%) with focal leakage who were treated with PDT had resolution of SRF ($P = .014$). Mean BCVA increase in the HSML treatment group, comparing baseline and evaluation visit 1, was 2.1 ± 7.3 ETDRS letters, whereas this was 5.1 ± 7.4 ETDRS letters for the PDT group ($P = .110$). When comparing baseline and final visit, the mean BCVA increase in ETDRS letters was 4.7 ± 8.1 in the HSML group and 8.1 ± 8.3 in the PDT group ($P = .140$).

Between baseline visit and evaluation visit 2, the mean SFCT decreased, with 37.3 ± 69.4 μm in the HSML treatment group and 57.4 ± 104.8 μm in the PDT group ($P = .639$). The mean decrease in SFCT comparing baseline and final visit was 41.3 ± 87.0 μm in the HSML treatment group and 60.1 ± 112.9 μm in the PDT group ($P = .570$).The mean increase in retinal sensitivity on microperimetry between baseline and evaluation visit 1 was 1.2 ± 4.0 dB in the HSML treatment group and 3.1 ± 3.1 dB in the PDT group ($P = .048$). Between baseline and final visit, the mean increase in retinal sensitivity was 2.2 ± 5.3 dB in the HSML group and 4.4 ± 3.3 dB in the PDT group ($P = .079$). The results regarding the CFT, SFCT, and NEI-VFQ25 have been summarized in Table 2.

• **DIFFUSE LEAKAGE GROUP:** The results of the diffuse leakage group are summarized in Table 2. In the diffuse leakage group, 49 patients (52%) were treated with HSML treatment and 46 patients (48%) were treated with PDT. The mean age at baseline was 49 ± 8 years in the HSML subgroup and 51 ± 9 years in the PDT subgroup ($P = .474$). The mean duration of symptoms was 7.5 months in the HSML treatment subgroup, whereas it was 6.7 months for the PDT subgroup ($P = .378$). Of the patients treated with HSML, 8 (16%) had a complete resolution of SRF at evaluation visit 1, while 22 patients (48%) in the PDT group showed complete resolution of SRF ($P = .002$). The mean number of HSML treatment spots in the patients who had a successful response to HSML treatment was 273, compared with 222 spots in the patients with persistent SRF ($P = .590$). There were 61 patients in the diffuse leakage group who received a second treatment. Out of these 61 patients, 40 received HSML treatment and 21 received PDT. There were 3 patients (8%) in the HSML treatment group and 7 patients (33%) in the PDT group who showed complete resolution of SRF at the evaluation visit after the second treatment ($P = .024$). At final visit, 9 out of 42 patients (21%) that were treated with HSML treatment and attended the final visit had resolution of SRF, whereas 24 out of 42 patients (57%) that had a final visit after PDT had total resolution of SRF ($P = .002$). Mean change in BCVA in the HSML treatment group, comparing baseline and evaluation visit 1, was +0.9 ± 10.0 ETDRS letters, whereas this

TABLE 2. Characteristics of Patients With Chronic Central Serous Chorioretinopathy With Focal or Diffuse Leakage and Treated With Half-Dose Photodynamic Therapy or High-Density Subthreshold Micropulse Laser

Focal Leakage Group	HSML N (%)	Half-Dose PDT N (%)	*P* Value
Resolution of SRF			
Control visit 1 (n = 63)	5 (16.7%)	17 (56.7%)	.007[a]
Final visit (n = 55)	11 (40.7%)	21 (75.0%)	.014[a]
	Mean ± SD	Mean ± SD	*P* Value
BCVA increase in ETDRS			
Baseline-control visit 1 (n = 63)	2.1 ± 7.3	5.1 ± 7.4	.110
Baseline-final visit (n = 55)	4.7 ± 8.1	8.1 ± 8.3	.140
NEI-VFQ25 increase in composite score (points)			
Baseline-control visit 1 (n = 63)	2.2 ± 8.2	3.0 ± 6.2	.660
Baseline-final visit (n = 54)	3.3 ± 10.8	7.6 ± 9.4	.125
Retinal sensitivity increase (dB)			
Baseline-control visit 1 (n = 60)	1.2 ± 4.0	3.1 ± 3.1	.048[a]
Baseline-final visit (n = 50)	2.2 ± 5.3	4.4 ± 3.3	.079
CFT increase (μm)			
Baseline-control visit 1 (n = 62)	4.3 ± 15.6	1.7 ± 15.1	.500
Baseline-final visit (n = 54)	1.5 ± 24.4	12.0 ± 18.3	.079
SFCT decrease (μm)			
Baseline-control visit 1 (n = 62)	40.6 ± 83.1	42.8 ± 105.2	.078
Baseline-final visit (n = 45)	41.3 ± 87.0	60.1 ± 112.9	.570
Diffuse Leakage Group	**HSML N (%)**	**Half-Dose PDT N (%)**	***P* Value**
Resolution of SRF			
Control visit 1 (n = 95)	8 (16.3%)	22 (47.8%)	.002[a]
Final visit (n = 84)	9 (21.4%)	24 (57.1%)	.002[a]
	Mean ± SD	Mean ± SD	*P* Value
BCVA increase in ETDRS			
Baseline-control visit 1 (n = 95)	0.9 ± 10.0	4.4 ± 6.1	.049[a]
Baseline-final visit (n = 85)	4.1 ± 6.7	5.6 ± 8.8	.379
NEI-VFQ25 increase in composite score (points)			
Baseline-control visit 1 (n = 94)	3.0 ± 6.8	2.8 ± 9.7	.891
Baseline-final visit (n = 85)	5.8 ± 8.8	6.7 ± 12.0	.679
Retinal sensitivity increase (dB)			
Baseline-control visit 1 (n = 91)	0.8 ± 3.5	1.3 ± 2.8	.447
Baseline-final visit (n = 77)	1.0 ± 3.8	2.7 ± 3.3	.036[a]
CFT increase (μm)			
Baseline-control visit 1 (n = 95)	3.3 ± 16.2	5.5 ± 18.7	.551
Baseline-final visit (n = 82)	4.5 ± 21.8	8.0 ± 21.1	.079
SFCT decrease (μm)			
Baseline-control visit 1 (n = 70)	15.8 ± 93.8	64.6 ± 73.8	.019[a]
Baseline-final visit (n = 59)	10.4 ± 86.5	78.3 ± 73.9	.002[a]

BCVA = best-corrected visual acuity; CFT = central foveal thickness; ETDRS = Early Treatment of Diabetic Retinopathy Study; HSML = high-density subthreshold micropulse laser; NEI-VFQ25 = National Eye Institute Visual Function Questionnaire 25-items; PDT = photodynamic therapy; RPEA = retinal pigment epithelium alterations; SD = standard deviation; SFCT = subfoveal choroidal thickness; SRF = subretinal fluid.

[a]*P* values <.05 were deemed statistically significant.

was +4.4 ± 6.1 ETDRS letters for the PDT group (*P* = .049). The mean change in BCVA comparing baseline and final visit was +4.1 ± 6.7 ETDRS letters in the HSML treatment group, compared with +5.6 ± 8.8 ETDRS letters in the PDT group (*P* = .379).

The mean increase in retinal sensitivity on microperimetry between baseline and evaluation visit 1 was 0.8 ± 3.5 dB in the HSML treatment group and 1.3 ± 2.8 dB in the PDT group (*P* = .447). The mean increase in retinal sensitivity between baseline and final visit was 1.0 ± 3.8 dB in

the HSML treatment group and 2.7 ± 3.3 dB in the PDT group ($P = .036$). The results of the CFT, SFCT, and NEI-VFQ25 are shown in Table 2.

DISCUSSION

BASED ON THE RESULTS OF THIS STUDY, HALF-DOSE PDT was shown to be superior to HSML treatment in inducing a complete resolution of SRF in cCSC patients, irrespective of a focal or diffuse leakage pattern on FA. The current study, a subgroup analysis of the PLACE trial, was in principle not powered to detect significant differences between anatomic and functional endpoints, because a power calculation to detect significant differences in such clinical endpoints between the treatments was only performed for the complete group of cCSC patients in the PLACE trial. However, apart from the superiority of PDT in inducing a complete SRF resolution on OCT (anatomic success) in the focal and diffuse leakage subgroups of cCSC, statistically significant differences in functional outcome in favor of PDT were detected in both subgroups. In patients with diffuse leakage, PDT resulted in a significantly higher decrease in SFCT and increase in retinal sensitivity from baseline to final visit, compared with patients treated with HSML. In addition, there was a significantly higher increase in BCVA between baseline and evaluation visit 1 in the diffuse leakage subgroup treated with PDT compared with those treated with HMSL.

Apart from BCVA, retinal sensitivity is an important sensitive and functional parameter in cCSC, as recovery of the BCVA can be delayed after cCSC treatment, and the baseline BCVA in cCSC is already relatively high.[32] An increase in the CFT was present in both treatment groups, which is in line with previously published literature, and could have been due to restoration of the neuroretina in successfully treated patients.[20,33] Despite the fact that virtually all other functional parameters (such as the NEI-VFQ25 questionnaire) were not statistically significantly different between HSML treatment and PDT, there was a clear trend of these parameters showing a higher increase in the PDT subgroup in both the focal and diffuse leakage subgroups.

In cCSC, choroidal dysfunction is presumed to be the primary underlying pathophysiological mechanism.[1,3] The superiority of PDT over HSML treatment in both the focal and diffuse leakage group could indicate that extensive choroidal abnormalities may be present in both groups, since PDT mainly has an effect on choroidal structure and function, whereas HSML treatment has been postulated to mainly affect the RPE.[24] Although patients with focal leakage in this study had a maximum of 1 "hot spot" of leakage on FA, more extensive choroidal abnormalities can already be present and may not be limited to the area of fluorescein leakage on FA, which could explain the superiority of PDT over HSML treatment in this study.

Interestingly, a significant reduction of the SFCT after treatment with PDT was only observed in the diffuse leakage group. Remodeling of the choroid induced by PDT has been found to lead to a reduction in SFCT. The mechanism is unclear, but may involve transient ischemia in the choriocapillaris.[22,34] Choroidal dysfunction may be more extensive in cCSC patients with diffuse leakage as opposed to patients with focal leakage, which could have an effect on the SFCT decrease and treatment response. This may be in contrast with cCSC patients with focal leakage on FA, in which hyperpermeability of the choroid may be only present at the hot spot of leakage on FA. However, choroidal abnormalities can also be (much) more extensive than FA abnormalities, in which case the hot spot of FA leakage can be considered a focal eruption of a larger underlying smoldering process of choroidal thickening (pachychoroid) and dysfunction. No significant difference between the focal and diffuse leakage group was observed regarding the exact location and size of the PDT-treated anatomic area, which excluded a possible bias, since SFCT was only measured foveally. The abnormalities on FA are by definition less extensive in the focal leakage group as compared with the diffuse leakage group, but abnormalities on ICGA have been reported to be often larger than those observed on FA.[35] However, it is unknown if abnormalities on FA are directly linked to the extent of abnormalities on ICGA.

This study has limitations. The categorization of patients into a focal and diffuse leakage group can be considered somewhat arbitrary, since it was based on clinical experience and previous published articles, and owing to a lack of uniform classification of cCSC to date.[1,3,29,36] With regard to the SFCT measurements, there were patients in whom the scleral border was insufficiently detectable on EDI-OCT imaging, and these images therefore had to be excluded. Excluding these patients may have introduced a bias, since these patients in particular may have a thickened choroid that may have hindered visibility of the scleral border and SFCT analysis. Therefore, the SFCT results should be interpreted with caution. In this study, only patients who used corticosteroids in the past 3 months were excluded. Other pharmacologic potential triggers for CSC, such as antibiotic use, amphetamine derivatives, and phosphodiesterase inhibitors, have not been excluded because of ambiguity or paucity of evidence, but might have had an effect on the treatment outcome.[37–41] The first evaluation visit of 6 weeks after treatment may be a little soon to evaluate the effect of PDT, since the full effect of treatment may not be achieved yet. However, the results indicate that even at 6 weeks PDT leads to a significantly higher number of patients with a complete resolution of SRF compared with HSML treatment, with this still being significant

at final follow-up 7-8 months after treatment. Physicians who perform HSML treatment are unable to determine the areas already treated with HSML, and therefore the results of this study only apply to the HSML treatment protocol that was used in this study. In addition, the PLACE trial data that were used in this study were not powered for the sub-analyses of cCSC patients with focal or diffuse leakage on FA. Despite this limitation, we found some significant differences between PDT and HSML treatment outcomes in the 2 subgroups, in favor of PDT. Therefore, larger studies are needed to further investigate potential differences in functional outcomes.

Although the number of HSML spots used in this study is lower compared with some other studies, undertreatment was unlikely, since HSML treatment was ICGA-guided and covered relatively large surfaces, with high power settings.[18,42] The success rate with regard to complete resolution of SRF and BCVA increase was lower in this study, compared with previous literature.[16–18] However, this previous literature is based on retrospective or nonrandomized studies with imbalances in baseline characteristics, which makes it difficult to compare treatment effects. Additionally, the studies performed by Scholz and associates[32] and Arsan and associates[42] comprised patients who had previously received other cCSC treatments such as PDT or anti-VEGF. Moreover, there is no standardized protocol for HSML treatment, making it difficult to compare these studies. Interestingly, Chen and associates found a less favorable response to HSML treatment in diffuse cCSC compared with focal cCSC.[25] According to the results of the focal leakage group in our study, HSML treatment did not lead to the same success rate as reported in the focal leakage group by Chen and associates. These discrepancies may be due to the small sample size, different HSML settings, differences in inclusion criteria, or the nonrandomized nature of previous studies. This emphasizes the need for standardized HSML settings and prospective, large randomized controlled trials for cCSC, such as the PLACE trial, which was used for the analyses in the current study.

This is the first study based on a relatively large randomized controlled trial in which the effect of PDT and HSML treatment is analyzed in patients based on either focal or diffuse leakage on FA. Both focal and diffuse cCSC may probably be viewed as expressions of the same disease entity, particularly since PDT was found to be superior to HSML treatment in both subgroups. Based on the results of this study, half-dose PDT is the preferred treatment over HSML for cCSC patients, both with focal and with diffuse leakage on FA.

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