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# EFFICACY OF HALF-DOSE PHOTODYNAMIC THERAPY VERSUS HIGH-DENSITY SUBTHRESHOLD MICROPULSE LASER FOR TREATING PIGMENT EPITHELIAL DETACHMENTS IN CHRONIC CENTRAL SEROUS CHORIORETINOPATHY

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**Purpose:** Comparing the effect of half-dose photodynamic therapy and high-density subthreshold micropulse laser treatment on retinal pigment epithelial detachments (PEDs) in chronic central serous chorioretinopathy.

**Methods:** This study included data from the PLACE trial, a prospective randomized controlled trial comparing half-dose photodynamic therapy and high-density subthreshold micropulse laser treatment in chronic central serous chorioretinopathy. Main outcome measurements were changes in both the foveal PED and the highest PED within the macula at baseline compared with first and final evaluation visit.

**Results:** At baseline, a macular PED was detected in 76.9% of patients (123/160), and a PED within 1,500  $\mu\text{m}$  from the foveal center in 37.5% of patients (60/160). In the half-dose photodynamic therapy arm (61 patients), there was a significantly larger decrease in the highest macular PED compared with the high-density subthreshold micropulse laser treatment arm (62 patients) at both first and final evaluation visits ( $P < 0.001$  and  $P = 0.012$ , respectively). The decrease of highest foveal PED was significant at first visit ( $P = 0.025$ ).

**Conclusion:** Half-dose photodynamic therapy is superior to high-density subthreshold micropulse laser treatment with regard to a statistically significant reduction in the height of macular PEDs in active chronic central serous chorioretinopathy. These findings may also have implications for other diseases within the pachychoroid disease spectrum that can present with PEDs.

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Central serous chorioretinopathy (CSC) is considered the fourth most common maculopathy in which subretinal fluid (SRF) occurs after neovascular age-related macular degeneration, diabetic macular edema, and retinal venous occlusion. In CSC, this fluid is usually located in the macula, which may induce visual complaints such as vision loss, diminished color

and contrast vision, and metamorphopsia.<sup>1</sup> These symptoms can severely affect the quality of life of often relatively young patients.<sup>2</sup> Although acute CSC usually resolves spontaneously without the need of treatment, chronic CSC (cCSC) may persist and lead to irreversible vision loss.<sup>3–6</sup> Several risk factors have been described for CSC, including age, male sex,

pregnancy, and corticosteroid use.<sup>1</sup> The pathophysiology of CSC is not fully understood. However, choroidal abnormalities, such as delayed choroidal filling, dilated veins, intervortex venous anastomoses, and choroidal vascular hyperpermeability, have been hypothesized to be an important underlying factor, with subsequent damage to the retinal pigment epithelium (RPE) and SRF accumulation.<sup>1,7,8</sup>

Several studies have shown that pigment epithelial detachments (PEDs) on spectral domain optical coherence tomography (OCT) are present in 53% to 96% of affected eyes of patients with CSC.<sup>2,9,10</sup> In most studies, these PEDs are defined as a distinct separation of the RPE from the underlying Bruch membrane.<sup>11</sup> In CSC, PEDs can be observed either inside or outside the area in which SRF has accumulated. The PEDs are often seen in areas with dilated choroidal vessels and increased choroidal

thickness, which suggests that PEDs—at least in CSC—may also be a result of underlying choroidal dysfunction.<sup>1,9,11</sup>

In cCSC, treatment is generally advocated because significant visual symptoms, a decreased quality of life, and progressive vision loss may occur in case of persistent SRF.<sup>2,4,6</sup> Half-dose photodynamic therapy (PDT) and high-density subthreshold micropulse laser (HSML) treatment are two of the most frequently used treatments in CSC.<sup>12</sup> Treatment should be aimed at a complete resolution of SRF to restore the normal anatomical and functional photoreceptor–RPE interaction.<sup>12</sup> Ample retrospective studies are available on the treatment of CSC, but these are vulnerable to scientific flaws especially in CSC, in which a spontaneous decrease of SRF is common and even a complete resolution of SRF may occur in up to 30% of placebo-treated patients.<sup>12–14</sup> To date, two large prospective multicenter randomized controlled trials on the role of PDT for the treatment of cCSC have been published, the PLACE trial Half-Dose Photodynamic Therapy versus High-Density Subthreshold Micropulse Laser Treatment in Patients with Chronic Central Serous Chorioretinopathy and the SPECTRA trial (Half-Dose Photodynamic Therapy Versus Eplerenone: Treatment Trial for Chronic Central Serous Chorioretinopathy). The SPECTRA trial concluded that both functional and anatomical outcomes improved significantly more after half-dose PDT compared with treatment with oral eplerenone.<sup>15</sup> The PLACE trial showed that half-dose PDT is superior to HSML treatment with regard to achieving a complete resolution of SRF and functional improvement.<sup>16</sup> The superiority of half-dose PDT over HSML treatment appears to originate in the fact that PDT treats the choroid, which is presumed to be the primary involved structure in cCSC.<sup>12</sup> The hyperfluorescent abnormalities present on indocyanine green angiography (ICGA) are used to guide the PDT spot.<sup>12,16</sup> PDT treats the thickened and leaky choroid in cCSC, causing choroidal remodeling and a choroidal thickness that is closer to the normal range.<sup>17,18</sup> This may lead to a decreased flow of fluid through the damaged outer blood–retina barrier at the RPE, with subsequent resolution of SRF.<sup>12</sup> However, little is known regarding the efficacy of half-dose PDT versus HSML treatment regarding resolution of PEDs. Resolution of PEDs in cCSC may be important because PEDs have been associated with reduced visual acuity at both short-term and long-term follow-up visits.<sup>19</sup> In this study, we have evaluated the effect of half-dose PDT and HSML treatment on PEDs in cCSC.

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## Methods

For this study, we used data and multimodal imaging of patients with cCSC who were included in the PLACE trial. The PLACE trial was a randomized controlled treatment trial conducted at five academic medical centers located in the Netherlands, Germany, the United Kingdom, and France.<sup>16,20</sup> The study was conducted in accordance with the tenets of the Declaration of Helsinki, and all participating centers received approval from their respective institutional review board and ethics committee (ClinicalTrials.gov identifier: NCT01797861).

### Participants

The PLACE trial enrolled patients with cCSC with SRF that affected the fovea at baseline. Furthermore, these patients were required to have one or more regions of active focal leakage (“hot spots”) combined with RPE window defects on fluorescein angiography and compatible hyperfluorescent changes typical of cCSC on ICGA. This study only included patients with a visible PED within the grid on the 30° macular OCT scan at baseline visit. A PED was defined as any measurable separation of the RPE from the underlying Bruch membrane on OCT, with a homogeneously hyporeflective sub-RPE space.<sup>11</sup> Further inclusion and exclusion criteria for the PLACE trial are summarized in Table 1. The primary endpoint of the PLACE trial was the complete resolution of SRF on OCT at the first evaluation visit at 6 weeks to 8 weeks after treatment.<sup>16</sup>

### Procedures

At baseline visit of the PLACE trial, patients’ medical history and demographics were taken and an extensive ophthalmologic examination was performed. The latter consisted of assessing Early Treatment of

Diabetic Retinopathy Study best-corrected visual acuity (BCVA), retinal sensitivity on microperimetry, and vision-related quality of life using the National Eye Institute Visual Function Questionnaire. Fundus photographs, OCT scans, fundus autofluorescence, fluorescein angiography, and ICGA imaging were made by certified medical photographers in all participating centers. Patients were randomly assigned to receive either half-dose PDT or HSML treatment at a 1:1 ratio, as described in the original PLACE trial study.<sup>16</sup> For both HSML treatment and half-dose PDT, the area to be treated was determined by the central reading center based on hyperfluorescent areas on ICGA compatible with SRF on OCT and leakage on fluorescein angiography.

Before the start of treatment with either half-dose PDT or HSML treatment, the pupil of the eye to be treated was dilated with topical 2.5% phenylephrine (phenylephrine monofree; Théa Pharma, Haarlem, the Netherlands) and 1.0% tropicamide (tropicamide monofree; Théa Pharma, Haarlem, the Netherlands). Patients assigned to the half-dose PDT arm received an intravenous infusion of 3 mg/m<sup>2</sup> body surface verteporfin (Visudyne; Novartis Pharma AG, Basel, Switzerland) over 10 minutes. Then, an anesthetic drop containing oxybuprocaine 0.4% (oxybuprocaine monofree; Théa Pharma, Haarlem, the Netherlands) was given before placing a contact lens on the eye at exactly 15 minutes after the start of verteporfin administration. Subsequently, half-dose PDT was performed in the area to be treated with a fluency of 50 J/cm<sup>2</sup>, wavelength of 689 nm, and treatment duration of 83 seconds.

High-density subthreshold micropulse laser treatment was performed by applying several adjacent nonoverlapping spots using an 810-nm diode laser, keeping a distance of 500 μm from the foveal center. To minimize possible undertreatment, a relatively high power of 1,800 mW was applied with a duty cycle of

Table 1. Inclusion and Exclusion Criteria of Patients With Chronic Central Serous Chorioretinopathy Who Were Enrolled in This Study

Inclusion Criteria	Exclusion Criteria
1. Male or female patients with cCSC ≥18 years old	1. Previous treatments for CSC
2. Visual loss and/or presence of SRF on OCT >6 weeks	2. Intraretinal fluid
3. BCVA of >20/200 in Snellen equivalent	3. Myopia >6 diopters
4. Foveal SRF	4. Evidence of another diagnosis that could explain either vision loss or SRF
5. At least 1 hyperfluorescent area of leakage on FA with RPE window defects typical of cCSC	5. Continuous or progressive visual loss or presence of SRF >18 months
6. Hyperfluorescent areas on ICGA typical of cCSC	6. Currently treated or treated with corticosteroids within the last 3 months before screening visit
7. Sufficient quality of imaging	7. Presence of soft drusen or signs of neovascularization
8. Presence of PED within the grid on the 30 macular OCT scan at baseline visit	8. Contraindications to receive FA, ICGA, or PDT

cCSC, chronic central serous chorioretinopathy; FA, fluorescein angiography.

5% and frequency of 500 Hz.<sup>21</sup> The spot size was set to 125  $\mu\text{m}$  and exposure time to 0.2 seconds per spot. If any retinal discoloration appeared after applying a test treatment spot outside of the macular area, the power of HSML treatment was reduced in steps of 300 mW to accomplish the desired subthreshold treatment and in accordance with the most available literature on performing the optimal HSML treatment.<sup>12</sup>

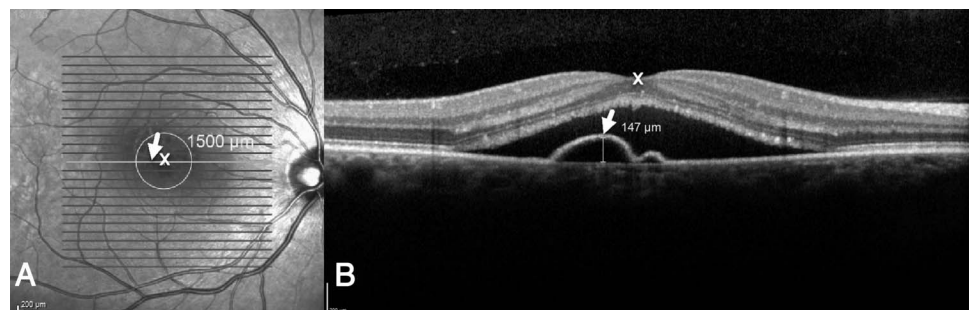
At the first evaluation visit at 6 weeks to 8 weeks after treatment and at final evaluation visit at 7 months to 8 months after first treatment, patients again underwent complete ophthalmologic examination and imaging. If SRF was still present within the macula area at first evaluation visit, the same treatment as the first treatment performed was performed.<sup>16</sup>

For patients to be included in this study, OCT scans were required to be available for baseline and at least one visit after treatment. Scans of insufficient quality that did not allow reliable measurement of the PED parameters described before were excluded from this study.

### Outcomes

Macular spectral domain OCT 30° images that were taken at baseline visit, first evaluation visit, and final evaluation visit were analyzed during this study. The Heidelberg built-in caliper tool was used to assess the height of the separation of the RPE from the underlying Bruch membrane with a homogeneously hyporeflective sub-RPE space, drawing a line perpendicular to the Bruch membrane (Figure 1). Any measurable separation with a homogeneously hyporeflective sub-RPE space was considered to be a PED, with no restrictions to dimension. Only the highest macular PED (hPED) within the grid on the 30° macular OCT scan and, if present, the highest foveal PED (fPED)—which was defined as the highest PED within a 1,500  $\mu\text{m}$  diameter from the foveal center—were measured. The percentage of patients with cCSC with complete resolution of the PED at final evaluation visit was recorded and compared between both treatment arms.

**Fig. 1.** Example measurement of a foveal PED in a 40-year-old patient with central serous chorioretinopathy. On the IR image (A), the foveal area, defined as a circle with a diameter of 1,500  $\mu\text{m}$  around the foveal center, is demarcated in white. The cross on the IR photograph (A) correlates with the location of the line on the spectral domain OCT image (B). The arrow indicates the location of the highest PED. The height of the hyporeflective lumen of the PED (line and measurement in  $\mu\text{m}$ ) (B) was measured perpendicularly to the Bruch membrane using the Heidelberg built-in caliper tool. IR, infrared reflectance.



### Statistical Analysis

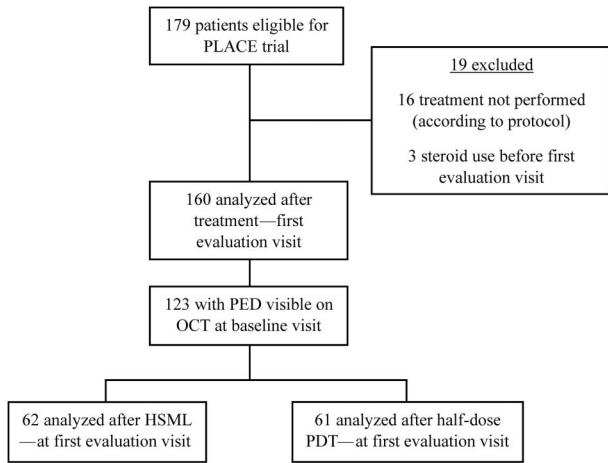
Statistical analysis was performed using IBM SPSS Statistics 23 (SPSS 23, IBM, New York, NY). For comparing baseline characteristics between the half-dose PDT and HSML treatment arm, the independent samples *t*-test was used apart from the PED presence and sex for which the chi-square test was used. A linear mixed model was used for testing the significance of change in PED height and functional parameters. The change in PED height was analyzed after logarithmic transformation because of its skewed distribution. The results were analyzed with an intention-to-treat analysis.

### Results

Of the 160 patients who were eligible for enrollment from the PLACE trial and had attended the first evaluation visit, a PED was detected at baseline visit in 123 patients (76.9%). Sixty-one patients with a PED at baseline had been randomized to the half-dose PDT arm and 62 to the HSML treatment arm. Of these 123 patients, 21 did not attend the final evaluation visit because they were lost to follow-up or did not receive a second treatment despite being indicated because of their personal preference. These patients were still analyzed in this study with an intention-to-treat analysis (Figure 2).

Baseline characteristics of the two groups were compared and are summarized in Table 2. There were no significant differences between the two groups at baseline. Of the 123 patients with a PED, 60 (48.8%) had a PED that also included the fovea. In 43 of these 60 patients with a fPED (71.7%), this fPED was also the hPED. Information about the received treatments is outlined in Table 3.

A decrease in the hPED height at first evaluation visit and final evaluation visit was seen in both the half-dose PDT-treated patients (median  $-6.50$  and  $-12.00$   $\mu\text{m}$ , respectively) and HSML-treated patients (median  $-1.00$  and  $-3.00$   $\mu\text{m}$ , respectively). The



**Fig. 2.** Flow chart depicting the patients with chronic central serous chorioretinopathy who have been included in this study.

median decrease in hPED height was significantly larger in the half-dose PDT arm compared with the HSML treatment arm at both first and final evaluation visits ( $P < 0.001$  and  $P = 0.012$ , respectively) (Table 4). A complete resolution of the hPED was seen in 13.0% of HSML-treated patients (7/54) and in 36.5% of half-dose PDT-treated patients (19/52) at final evaluation visit ( $P = 0.005$ ). Examples have been depicted in Figure 3. The mean decrease in hPED height at first evaluation visit and final evaluation visit was significantly larger in patients who had had a complete SRF resolution at first evaluation visit ( $P < 0.001$  and  $P = 0.001$ , respectively).

The median decrease in highest fPED at first evaluation visit in the half-dose PDT arm was significantly larger compared with the HSML treatment arm (median  $-6.00 \mu\text{m}$  vs. median  $-1.00 \mu\text{m}$ , respec-

tively) ( $P = 0.025$ ). However, the decrease of fPED was not significantly different between the groups at final evaluation visit ( $P = 0.065$ ) (Table 4). A complete resolution of the highest fPED was seen in 8.3% of the HSML-treated patients (2/24) and in 29.6% of the half-dose PDT-treated patients (8/27) ( $P = 0.056$ ).

At first evaluation visit, 54/62 (87.1%) of patients treated with HSML had a persistence of SRF compared with 34/61 (55.7%) of patients treated with half-dose PDT. At first evaluation visit, the odds of presence of SRF differed significantly between patients treated with HSML and half-dose PDT ( $P < 0.001$ ) and were 84.09% lower in the half-dose PDT treatment arm compared with the HSML treatment arm (odds ratio = 0.159 [95% confidence interval 0.058–0.437]). At the final evaluation visit, 35/52 (67.3%) of patients treated with half-dose PDT had a complete SRF resolution compared with 19/54 (35.2%) of patients in the HSML treatment arm. At this visit, the odds of presence of SRF did also differ significantly between the HSML treatment arm and the half-dose PDT treatment arm ( $P < 0.001$ ). These odds were 73.37% lower in the half-dose PDT treatment arm compared with the HSML treatment arm (odds ratio = 0.266 [95% confidence interval: 0.134–0.527]).

The functional outcome parameters after treatment (BCVA, retinal sensitivity on microperimetry, and the vision-related quality of life using the National Eye Institute 25-item Visual Function Questionnaire) did not differ significantly between the HSML-treated and half-dose PDT arm at both first evaluation visit and final evaluation visit, except for the BCVA at first evaluation visit, which improved significantly more in the half-dose PDT arm than the HSML treatment arm.

Table 2. Baseline Characteristics of Patients Included in This Study

	Half-Dose Photodynamic Therapy (n = 61)	High-Density Subthreshold Micropulse Laser Treatment (n = 62)	P
Age (years)	48.6 ± 9.0	48.7 ± 8.5	0.940
Male sex	46 (75.4%)	52 (83.4%)	0.244
BCVA in study eyes (ETDRS letters)	76.4 ± 9.0	75.6 ± 9.1	0.625
Composite score on vision-related quality of life measured with the NEI-VFQ25	81.6 ± 13.2	82.6 ± 11.6	0.653
Retinal sensitivity on microperimetry (dB)	19.3 ± 5.7	19.2 ± 5.5	0.913
Foveal sensitivity on microperimetry (dB)	16.2 ± 6.5	16.4 ± 6.5	0.876
fPED present	31 (50.8%)	29 (46.8%)	0.654
Height of hPED (μm)	41.3 ± 57.4 (range, 5.0–407.0)	42.0 ± 51.3 (range, 7.0–299.0)	0.945
Height of fPED (μm)	22.5 ± 53.9 (range, 9.0–389.0)	21.1 ± 47.6 (range, 6.0–299.0)	0.554
Foveal choroidal thickness (μm)	415.7 ± 123.0	414.7 ± 119.0	0.967

Data are either no. (%) or median (range) or mean ± SD.  $P$ -values  $< 0.05$  were considered to be statistically significant. NEI-VFQ25, National Eye Institute 25-item Visual Function Questionnaire.

Table 3. Characteristics of Received Treatments During This Study

	Half-Dose Photodynamic Therapy (n = 61)	High-Density Subthreshold Micropulse Laser Treatment (n = 62)
Mean diameter PDT spot in mm (first treatment)	4.05 ± 1.60	NA
Mean number of HSML treatment spots (first treatment)	NA	208.34 ± 224.61
Second treatment indicated/presence of SRF at first evaluation visit	34/61	54/62

### Discussion

To the best of our knowledge, this is the first study to assess the effect of half-dose PDT and HSML treatment on PEDs in cCSC based on a relatively large

prospective randomized controlled trial. Because prolonged detachment of the macula due to SRF accumulation can lead to irreversible vision loss because of photoreceptor and RPE atrophy, complete SRF resolution was considered the most important goal of

Table 4. Effect of Half-Dose Photodynamic Therapy Versus High-Density Subthreshold Micropulse Laser Treatment on the Highest Macular Pigment Epithelial Detachment and Foveal Pigment Epithelial Detachment

Outcome	Half-Dose Photodynamic Therapy	High-Density Subthreshold Micropulse Laser Treatment	P*
Height of hPED (μm)†			
At first evaluation visit	-6.50 (-21.00 to -1.00) (n = 61)	-1.00 (-5.50 to 1.25) (n = 62)	<0.001
At final evaluation visit	-12.00 (-26.00 to -4.00) (n = 52)	-3.00 (-15.00 to 3.00) (n = 54)	0.012
Height of fPED (μm)†			
At first evaluation visit	-6.00 (-21.00 to 0.00) (n = 31)	-1.00 (-4.50 to 1.00) (n = 29)	0.025
At final evaluation visit	-15.00 (-26.00 to -3.00) (n = 27)	-3.00 (-11.00 to 1.75) (n = 24)	0.065
BCVA in study eyes (ETDRS letters)‡			
At first evaluation visit	4.23 ± 5.95 (n = 61)	1.05 ± 9.89 (n = 62)	0.034
At final evaluation visit	6.00 ± 8.70 (n = 54)	4.44 ± 7.58 (n = 54)	0.190
Composite score on vision-related quality of life measured with the NEI-VFQ25‡			
At first evaluation visit	2.71 ± 8.81 (n = 61)	2.43 ± 7.57 (n = 61)	0.785
At final evaluation visit	7.07 ± 11.57 (n = 54)	5.32 ± 9.86 (n = 54)	0.707
Retinal sensitivity on microperimetry (dB) in study eyes‡			
At first evaluation visit	1.84 ± 3.16 (n = 58)	0.78 ± 3.44 (n = 59)	0.275
At final evaluation visit	3.31 ± 3.57 (n = 51)	1.57 ± 4.53 (n = 49)	0.117
Foveal sensitivity on microperimetry (dB) in study eyes‡			
At first evaluation visit	2.90 ± 5.34 (n = 51)	1.18 ± 6.22 (n = 51)	0.197
At final evaluation visit	4.48 ± 5.02 (n = 46)	2.05 ± 6.29 (n = 44)	0.137
Foveal choroidal thickness (μm) in study eyes‡			
At first evaluation visit	-46.31 ± 83.74 (n = 45)	-31.00 ± 97.73 (n = 45)	0.723
At final evaluation visit	-62.03 ± 94.09 (n = 37)	-26.11 ± 97.19 (n = 37)	0.145

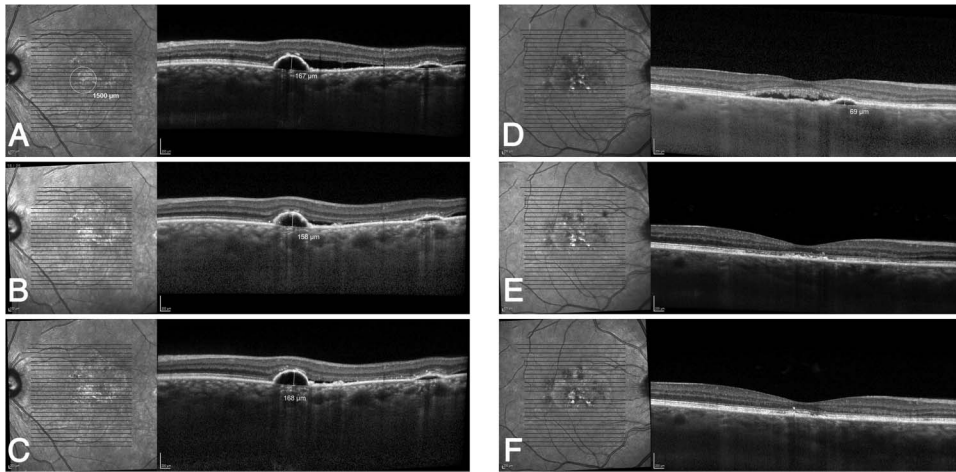
P-values <0.05 were considered to be statistically significant.

\*P-value for difference in effect on outcome comparing half-dose PDT and HSML treatment.

†Calculated with linear mixed model after logarithmic transformation. Data are expressed in median (interquartile range, Q1 and Q3) and n = number of patients analyzed.

‡Calculated with linear mixed model without logarithmic transformation. Mean (SD) and number of patients are analyzed. For these variables, the interaction term was not significant.

NEI-VFQ25, National Eye Institute 25-item Visual Function Questionnaire.



**Fig. 3.** Examples of the change in pigment epithelial detachment height of patients with chronic central serous chorioretinopathy after treatment. The OCT scans on the left part of the figure (A–C) belong to a 48-year-old patient with cCSC who had been treated with HSML. The OCT scan taken at baseline visit (A) shows a PED within the vascular arcades. The PED height remained relatively stable after treatment with HSML at first evaluation visit (B) and at final evaluation visit (C). Subretinal fluid was still present at the final evaluation visit (C). The OCT scans on the right side of the figure (D–F) belong to a 50-year-old patient with cCSC who had been treated with half-dose PDT.

At baseline visit (D), a PED could be seen within a diameter of 1,500  $\mu\text{m}$  around the foveal center. At first evaluation visit (E) and after treatment with half-dose PDT, both the subretinal fluid and the PED had disappeared. At final evaluation visit, SRF and the PED remained absent (F).

treatment.<sup>2,5,6</sup> However, it is also important to assess the effect of treatment on PEDs in cCSC because of the effect of dysfunction of the outer blood–retina barrier of the RPE on both anatomical and functional parameters.<sup>12,16</sup> After all, the RPE forms the “natural housekeeper” of the overlying photoreceptors, and a prolonged detachment of the RPE from the underlying choroid may in itself induce degenerative changes in the RPE, which is dependent on its physiologic relationship with the Bruch membrane/choroid complex.<sup>22</sup> Therefore, a desired treatment effect in cCSC may not only be the restoration of physiologic photoreceptor–RPE interaction but also the repositioning of the RPE in close association with the Bruch membrane and the adjacent multifunctional choroid.<sup>23</sup> Based on the results of this study, we conclude that half-dose PDT is more effective than HSML treatment in decreasing the height and inducing complete resolution of macular PEDs in cCSC on the short term and long term.

The available literature on the effect of PDT on PEDs in patients with cCSC is limited, but a few studies with relatively small numbers of included patients show that PDT has a positive effect on fovea-involving PEDs.<sup>24–26</sup> A retrospective study by Arf et al<sup>24</sup> showed a PED resolution in seven of 10 patients with cCSC after treatment with reduced-fluence PDT. In addition, Hwang et al<sup>25</sup> found that 80% of eyes ( $n = 35$ ) had a complete resolution of sub-fPED at 1 month after half-dose PDT. Finally, a study by Inoda et al<sup>26</sup> described a complete PED resolution in 8/12 (67%) of patients with a symptomatic serous nonneovascular PED after half-dose PDT. In the current cCSC cohort, we found a complete hPED resolution in 36.5% of patients (19/52), and a complete resolution of the highest fPED in 29.6% of patients

(8/27) after half-dose PDT, which are lower resolution rates compared with the aforementioned retrospective studies. This may be related to selection or publication bias of these retrospective studies, while we are the first to report this outcome with data from a randomized controlled treatment trial.

Functional parameters (BCVA, retinal sensitivity on microperimetry, and the vision-related quality of life using the National Eye Institute 25-item Visual Function Questionnaire) did not improve significantly more in the half-dose PDT-treated arm compared with the HSML-treated arm. These observations could have been caused by the already existing damage to the RPE and neurosensory retina because of the presence of SRF and a PED over a longer period of time. In addition, the PLACE trial was not powered to detect differences in these functional parameters for this specific study purpose, and BCVA, retinal sensitivity on microperimetry, and vision-related quality of life score measured by the National Eye Institute 25-item Visual Function Questionnaire were relatively high at baseline in patients with cCSC.

The mechanism of PDT is presumably based on the formation of free radicals on the laser illumination of the desired treatment site, which is mainly the choriocapillaris/choroid, after administering verteporfin intravenously. This may subsequently lead to remodeling of the vessels in the capillary bed and larger choroidal vessels that underlie the damaged RPE.<sup>12,17,27</sup> The superiority of half-dose PDT over HSML treatment could be explained by the fact that PDT targets the primary pathophysiological choroidal abnormalities in CSC by causing choroidal vascular remodeling.<sup>27</sup> By contrast, treatment with HSML has been suggested to mainly have



an effect on RPE function, and not the choroid, although the therapeutic mechanism of action, if any, of HSML treatment on the RPE is unclear, at least in cCSC.<sup>12,13,28</sup> With HSML treatment, laser spots are targeted on the hyperfluorescent abnormalities on ICGA. The laser energy has been hypothesized to be absorbed by the melanin in the RPE and results in the release of heat. This is believed to increase the expression of heat shock proteins, when applied in a sublethal dose, and restore the cellular function in the RPE.<sup>12</sup>

This study has limitations. First of all, the PLACE trial was originally powered to detect a potential difference in complete SRF resolution between half-dose PDT and HSML treatment and not to compare the treatment effect on PED characteristics measured in this study that used the PLACE trial data. All patients had SRF at baseline because this was an inclusion criterion for all patients with cCSC, which could have led to a bias in studying the treatment effect on PEDs in this specific subgroup.

Importantly, half-dose PDT may also be an effective treatment in treating symptomatic isolated PEDs in the context of a pachychoroid background (e.g., pachychoroid pigment epitheliopathy) because it may target the common pathophysiological background of choroidal dysfunction and vascular leakage to the space between the RPE and Bruch membrane.<sup>29,30</sup>

In conclusion, based on the results of this study, treatment with half-dose PDT, aimed at a complete resolution of SRF in patients with cCSC, is superior to HSML treatment with regard to reducing the height of macular PEDs. The outcome of this study may also have important implications for the treatment of PEDs in other diseases that are part of the pachychoroid spectrum.

**Key words:** central serous chorioretinopathy, half-dose photodynamic therapy, high-density subthreshold micropulse laser, pigment epithelial detachment, PLACE trial.

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