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Citation

Feenstra, H. M. A., Dijk, E. H. C. van, Rijssen, T. J. van, Tsonaka, R., Diederer, R. M. H., Schlingemann, R. O., ... Boon, C. J. F. (2022). Crossover to half-dose photodynamic therapy or eplerenone in chronic central serous chorioretinopathy patients. *Ophthalmology Retina*, 6(10), 930-938. doi:10.1016/j.oret.2022.04.014

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Note: To cite this publication please use the final published version (if applicable).

Crossover to Half-Dose Photodynamic Therapy or Eplerenone in Chronic Central Serous Chorioretinopathy Patients

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Purpose: To compare the efficacy and safety of crossover treatment to half-dose photodynamic therapy (PDT) and eplerenone treatment after the failure of primary treatment in patients with chronic central serous chorioretinopathy (cCSC).

Design: Multicenter crossover clinical trial.

Subjects: At 3 months after the baseline visit of the SPECTRA (Half-Dose Photodynamic Therapy Versus Eplerenone: Treatment Trial for Chronic Central Serous Chorioretinopathy) randomized controlled trial, either half-dose PDT or eplerenone treatment was evaluated for each patient, and patients who still demonstrated subretinal fluid (SRF) were included in the current study, the SPECS (Central Serous Chorioretinopathy Treated with Half-Dose PDT or Eplerenone Crossover Study) trial.

Methods: At the baseline visits for the current SPECS trial, crossover treatment was performed for patients who still demonstrated SRF. These patients received either half-dose PDT or oral eplerenone for 12 weeks. Both anatomic and functional parameters were evaluated 3 months after crossover treatment.

Main Outcome Measures: Complete resolution of SRF on OCT.

Results: Forty-nine patients were included in the SPECS trial (38 received primary eplerenone treatment; 11 received half-dose PDT). At 3 months after crossover treatment, 32 of 37 (86.5%) in the crossover to half-dose PDT group and 2 of 9 (22.2%) in the crossover to eplerenone group had complete SRF resolution ($P = 0.030$). The mean foveal sensitivity increased significantly more in the crossover to half-dose PDT group (mean, +3.08 dB) compared with the crossover to eplerenone group (mean, -0.27 dB; $P = 0.009$).

Conclusions: Patients with cCSC with the persistence of SRF after primary eplerenone treatment can benefit from half-dose PDT, which can induce a relatively fast and complete SRF resolution, along with an improvement in foveal sensitivity. *Ophthalmology Retina* 2022;6:930-938 © 2022 Published by Elsevier Inc. on behalf of the American Academy of Ophthalmology



Supplemental material available at www.opthalmologyretina.org.

Central serous chorioretinopathy (CSC) is the fourth—most common primary maculopathy and is associated with the loss of central vision, metamorphopsia, and diminished color and contrast vision.¹ Central serous chorioretinopathy is characterized by the accumulation of subretinal fluid (SRF), which is typically located under the macula. The pathophysiology of CSC is not fully understood, but SRF accumulation is thought to be secondary to choroidal abnormalities that induce damage to the outer blood—retina barrier at the level of the retinal pigment epithelium (RPE).^{2,3} Risk factors for CSC include male sex, the use of corticosteroids, genetic risk variants, and pregnancy.^{1,4–7}

Central serous chorioretinopathy can be roughly divided into acute and chronic CSC (cCSC) depending on the duration of disease and abnormalities on multimodal

imaging, although the classification is subject to controversy.⁸ Acute CSC, with a focal leak with very few atrophic RPE abnormalities, usually resolves within several months, without the need for treatment, although the disease may recur.⁹ However, cCSC can lead to irreversible damage to the RPE and photoreceptors, vision loss, and reduced quality of life.^{10–12}

Many different treatment options for cCSC have been proposed, some with very limited evidence.¹ The evidence from retrospective studies is problematic, especially with respect to CSC—for example, because of highly variable inclusion criteria, publication bias, and the tendency to show a waxing and waning clinical course and spontaneous SRF resolution.^{1,9,13} In the VICI (Eplerenone for Chronic Central Serous Chorioretinopathy in Patients with Active, Previously Untreated Disease for More than

4 Months) randomized controlled trial, even patients with cCSC were found to have the spontaneous resolution of SRF on OCT in 30% of the placebo-treated patients after 1 year.¹⁴ To date, comparatively, 4 large, prospective randomized controlled trials have been published on the treatment of cCSC. Based on these 4 trials and many other retrospective studies, half-dose (or half-fluence) photodynamic therapy (PDT) seems to be the treatment of choice for cCSC when it is available.^{1,14–17} First of all, the PLACE (Half-Dose Photodynamic Therapy versus High-Density Subthreshold Micropulse Laser Treatment in Patients with Chronic Central Serous Chorioretinopathy) trial, which included 179 patients, showed that 67% of patients with cCSC treated with half-dose PDT and 29% of patients with cCSC treated with high-density subthreshold micropulse laser treatment had the complete resolution of SRF on OCT at 7 to 8 months. Importantly, in the PLACE trial, the functional outcome after half-dose PDT was superior to that after high-density subthreshold micropulse laser treatment; at 6 to 8 weeks after treatment, the half-dose PDT–treated patients showed significantly higher increases in best-corrected visual acuity (BCVA) and significantly higher increases in retinal sensitivity on microperimetry. Seven to 8 months after treatment, only the retinal sensitivity on microperimetry showed significantly greater improvements in the half-dose PDT–treated patients compared with the patients treated with the high-density subthreshold micropulse laser.¹⁵ In the Crossover to Photodynamic Therapy or Micropulse Laser After Failure of Primary Treatment of Chronic Central Serous Chorioretinopathy (REPLACE) trial, patients who had the persistence of SRF on OCT after the failure of primary treatment within the PLACE trial received crossover treatment with either a high-density subthreshold micropulse laser or half-dose PDT. The crossover to half-dose PDT after previous unsuccessful high-density subthreshold micropulse laser treatment for cCSC significantly improved anatomic and functional end points, whereas the crossover to high-density subthreshold micropulse laser after half-dose PDT did not show an improvement in any functional outcome parameters at the final follow-up of this study.¹⁶ In the third large randomized controlled trial on the treatment of cCSC, the VICI trial, the oral administration of the mineralocorticoid receptor (MR) antagonist eplerenone was not superior to placebo in terms of structural or functional improvement, with only 16% of eplerenone-treated patients achieving the complete resolution of SRF on OCT after 12 months.¹⁴ Thus, the VICI investigators recommended stopping the prescription of eplerenone for the treatment of cCSC. Lastly, in the SPECTRA (Half-Dose Photodynamic Therapy Versus Eplerenone: Treatment Trial for Chronic Central Serous Chorioretinopathy) trial, we compared oral eplerenone treatment to half-dose PDT in 107 patients with cCSC. Three months after randomization and treatment, 78% of the patients in the half-dose PDT group had the complete resolution of SRF on OCT, compared with only 17% of patients in the eplerenone group. In addition, the mean retinal sensitivity on microperimetry improved significantly more in the half-dose PDT group than in the eplerenone group.¹⁷

Thus far, it has been unknown if patients who were previously treated unsuccessfully with oral eplerenone may

benefit from crossover treatment to half-dose PDT and vice versa. In the current trial, we prospectively evaluated the efficacy of crossover treatment when primary treatment with either eplerenone or half-dose PDT in the SPECTRA trial was unsuccessful.

Methods

The SPECS (Central Serous Chorioretinopathy Treated with Half-Dose PDT or Eplerenone Crossover Study) resulted from the randomized controlled SPECTRA trial ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03079141) identifier NCT03079141), of which the protocol and results have been previously published.¹⁷ Patients were included from 3 academic medical centers located in the Netherlands: Leiden University Medical Center (Leiden), Amsterdam University Medical Centers (Amsterdam), and Radboud University Medical Center (Nijmegen). This study adhered to the tenets of the Declaration of Helsinki, and written informed consent was obtained from all participants at the start of the SPECTRA trial for the course of the entire study. Institutional review board/ethics committee approval was obtained from all participating centers before the start of the study.

Participants

In the original SPECTRA trial, patients over the age of 18 years who had cCSC and foveal SRF on OCT were randomly assigned (at a 1:1 ratio, using a web-based random numbers generator with block randomization) to either treatment with oral eplerenone (25 mg once daily for 1 week and 50 mg once daily for 11 weeks) or half-dose PDT. Subjective disease-related visual loss had to be present for at least 6 weeks but not longer than 18 months. At least 1 area of leakage had to be present on fluorescein angiography (FA), along with RPE window defects as a sign of chronicity. In these patients, hyperfluorescence on indocyanine green angiography (ICGA) had to correspond to FA and OCT abnormalities. The exclusion criteria included treatment with corticosteroids, either within 3 months before the start of the trial or during the trial; evidence of another disease that could explain the presence of SRF; myopia > 6 diopters; serum potassium level of > 5.5 mEq/L and/or creatinine clearance of ≤ 30 mL/min; the presence of either chorioretinal atrophy or drusen; the presence of intraretinal fluid on OCT; and signs of choroidal neovascularization on multimodal imaging at baseline. Three months after the patients received their assigned treatment, the presence of SRF on OCT was evaluated. If SRF was present on the OCT at this first evaluation visit (evaluation visit 1), then the patient was eligible for crossover treatment and could be included in the current trial.¹⁷

Procedures

At the baseline visits of the SPECTRA trial, patients' self-reported medical histories and demographics were taken. For each patient, an extensive ophthalmic examination, including BCVA measurement in ETDRS letters, the assessment of retinal sensitivity on microperimetry using the MAIA microperimeter (CenterVue), and the National Eye Institute Visual Functioning Questionnaire 25 (NEI VFQ-25) score, was performed at baseline, at evaluation visit 1 (SPECS baseline evaluation visit), and at 3 months after crossover treatment (evaluation visit 2 or SPECS posttreatment evaluation visit), if applicable. Moreover, fundus photographs, fundus autofluorescence imaging, OCT, FA, ICGA, and OCT angiography were obtained at baseline and both evaluation visits 1 and 2. All clinicians and photographers involved in the data collection were

trained and certified, and the data were obtained according to standard operating procedures.¹⁷

Half-Dose PDT

Each patient assigned to the half-dose PDT group received an IV infusion of 3 mg/m² body surface verteporfin within 10 minutes. Then, an anesthetic drop was given before a contact lens was placed on the eye exactly 15 minutes after the start of the verteporfin administration. Subsequently, half-dose PDT was performed in the area to be treated, with a fluency of 50 J/cm², wavelength of 689 nm, and treatment duration of 83 seconds. The area that had to be treated was determined based on the hyperfluorescent area(s) on midphase (10–15 minutes) ICGA, which corresponded to the SRF on OCT and hyperfluorescent leakage points on the midphase (approximately 3 minutes) FA. The spot size was defined based on the diameter of the hyperfluorescent area(s) on ICGA plus 1 mm, and the PDT spot had to be at least 200 µm away from the optic disc rim.¹⁷

Eplerenone Treatment

Treatment with eplerenone began with 25-mg eplerenone once daily for the first week. The patients' serum potassium levels were assessed during this first week of treatment. After 1 week of treatment, the eplerenone dose was increased to 50 mg daily when the serum potassium level was < 5.0 mEq/L, whereas the dosage of 25 mg once daily was continued when the serum potassium level was 5.0 to 5.4 mEq/L. When the serum potassium level was 5.5 to 5.9 mEq/L, the eplerenone treatment was decreased to 25 mg every other day, and when the serum potassium level was > 6.0 mEq/L, the eplerenone treatment was ceased. The serum potassium level was tested again 1 month after the initiation of eplerenone treatment, and this was repeated at monthly intervals. If needed, the eplerenone treatment dose was adjusted according to the serum potassium level during follow-up. Patients were instructed to return any remaining eplerenone tablets at the first visit to the clinic after the completion of the treatment.¹⁷

Clinical End Points

The primary end point for SPECS, like in the PLACE and SPECTRA trials, was the complete resolution of SRF on OCT. The secondary end points were the BCVA in ETDRS letters; the foveal and retinal sensitivities in dB on microperimetry; and the NEI VFQ-25 score. Both the primary and secondary end points were measured at the SPECS baseline evaluation visit (corresponding to SPECTRA trial evaluation visit 1) and at the SPECS posttreatment evaluation visit (at 3 months after crossover treatment, corresponding to SPECTRA trial evaluation visit 2). The NEI VFQ-25 responses were converted to scores between 0 and 100.

Any adverse events were reported to the principal investigator and the data safety monitoring board within 24 hours. If deemed necessary, the safety monitoring board had the option to terminate the study prematurely.¹⁷

Statistical Analysis

A test for the difference of proportions using 80% power and a significance level of $\alpha = 0.05$ was used to calculate a target sample size of 107 patients, allowing for a 25% dropout rate. The statistical analysis was performed using both R (version 4.0.1; R Foundation for Statistical Computing) and SPSS statistics (version 25.0; IBM Corp). The primary end point (binary longitudinal outcome of SRF on OCT) was analyzed using a mixed-effects logistic regression model. This analysis was performed by using the function `mixed_model(.)` from the R

package GLMMadaptive. Continuous longitudinal end points, such as the BCVA, foveal and retinal sensitivity on microperimetry, and NEI VFQ-25 score, were analyzed using a linear mixed-effects mixed model.

Results

Out of the 107 patients with cCSC who were originally included in the SPECTRA trial from February 22, 2017, to August 28, 2019, 96 were evaluated at the SPECTRA trial evaluation visit 1 (Fig 1). Thirteen patients were either lost to follow-up or did not adhere to the study protocol. The persistence of SRF on OCT at 3 months after primary treatment (SPECTRA trial evaluation visit 1) was present in 11 of 50 (22%) patients treated with half-dose PDT and in 38 of 46 (82.6%) patients treated with eplerenone. None of these patients had evidence of additional pathologies, such as choroidal neovascularization, on multimodal imaging, including OCT angiography, at the time of this evaluation visit. These 49 patients with cCSC with persistent SRF on OCT after primary half-dose PDT or eplerenone treatment could be included in the current SPECS trial and received crossover treatment within 4 weeks after the SPECTRA trial evaluation visit 1. All patients received crossover treatment before the verteporfin shortage occurred, and this, therefore, did not affect the decision to treat the patients according to the study protocol. The baseline characteristics of these patients are summarized in Table 1.

At the posttreatment evaluation visit (3 months after crossover treatment), 32 of 37 (86.5%) patients in the crossover from eplerenone to half-dose PDT group and 2 of 9 (22.2%) in the crossover from half-dose PDT to eplerenone group had the complete resolution of SRF on OCT ($P = 0.030$; Figs 2 and 3). The odds ratio (OR) of persistent SRF on OCT after crossover treatment with eplerenone was 15.5 times higher than that after treatment with half-dose PDT (95% confidence interval, 1.29–185.09; $P = 0.030$). The probability of the presence of SRF at the posttreatment evaluation visit only decreased significantly in the group of patients who received crossover treatment with half-dose PDT after previous persistent SRF after primary eplerenone treatment (OR, 0.0040; $P = 0.017$), which was in contrast with the crossover treatment with eplerenone after previous half-dose PDT (OR, 0.0614; $P = 0.063$; Table 2).

The mean foveal sensitivity increased significantly more in the crossover to half-dose PDT group (mean, +3.08 dB) compared with the crossover to eplerenone group (mean, −0.27 dB; $P = 0.009$). Within the crossover to half-dose PDT group, this increase was statistically significant ($P < 0.001$), but within the crossover to eplerenone group, it was not statistically significant ($P = 0.810$). The mean BCVA increased by 0.73 ETDRS letters between the baseline evaluation visit and the posttreatment evaluation visit in the crossover to eplerenone group and by 1.80 ETDRS letters in the crossover to half-dose PDT group; this difference in the BCVA improvement between the groups was not statistically significant ($P = 0.660$). The NEI VFQ-25 score increased in both the crossover to eplerenone group and the crossover to half-dose PDT group between the baseline evaluation visit and the posttreatment evaluation visit (mean, +1.48; $P = 0.555$ and +1.77; $P = 0.158$, respectively). Three patients could not be evaluated at the posttreatment evaluation visit because of loss to follow-up, the use of corticosteroids, or the withdrawal of consent (Fig 1).

Table 1. Baseline Characteristics of Patients with Central Serous Chorioretinopathy Who Received Crossover Treatment at the SPECS Trial Baseline Evaluation Visit

	Crossover from Eplerenone to Half-Dose PDT (n=38) Mean ± SD	Crossover from Half-Dose PDT to Eplerenone (n = 11) Mean ± SD	P Value
Age (yrs)	47.2 ± 10.4	46.0 ± 7.2	0.663
Best-corrected visual acuity (ETDRS letters)	83.3 ± 6.5 (n = 38)	72.2 ± 14.0 (n = 11)	0.026
NEI VFQ-25 score (points)	82.3 ± 12.4 (n = 38)	81.7 ± 10.7 (n = 11)	0.887
Retinal sensitivity (dB)	23.7 ± 3.3 (n = 36)	22.3 ± 4.5 (n = 10)	0.285
Foveal sensitivity (dB)	21.6 ± 3.5 (n = 36)	20.9 ± 4.2 (n = 9)	0.613
Sex			
Male	35 (92.1%)	11 (100%)	0.336

dB = decibels; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire 25; PDT = photodynamic therapy.

Adverse events occurred in 4 of 11 (36.4%) patients in the crossover to half-dose PDT group and in 3 of 38 (7.9%) patients in the crossover to eplerenone group (Table S1, available at www.opthalmologyretina.org, which illustrates the adverse events that occurred during SPECS). Of these patients, the possibly treatment-related side effects of half-dose PDT were itchiness of the eyelid in 1 patient and vasovagal reaction during FA in 1 patient. Possibly related side effects of eplerenone included fatigue and paresthesia of the hand and leg in 2 patients. One patient who received crossover treatment with eplerenone presented with a neovascularization at the posttreatment

evaluation visit. On retrospective re-evaluation, a small, flat, irregular pigment epithelial detachment, suggestive of a subtle type 1 choroidal neovascularization, was already present at the baseline visit of the SPECTRA trial. There were no serious adverse events.

Discussion

The preferential treatment of cCSC is subject to debate, although increasingly solid prospective evidence clearly

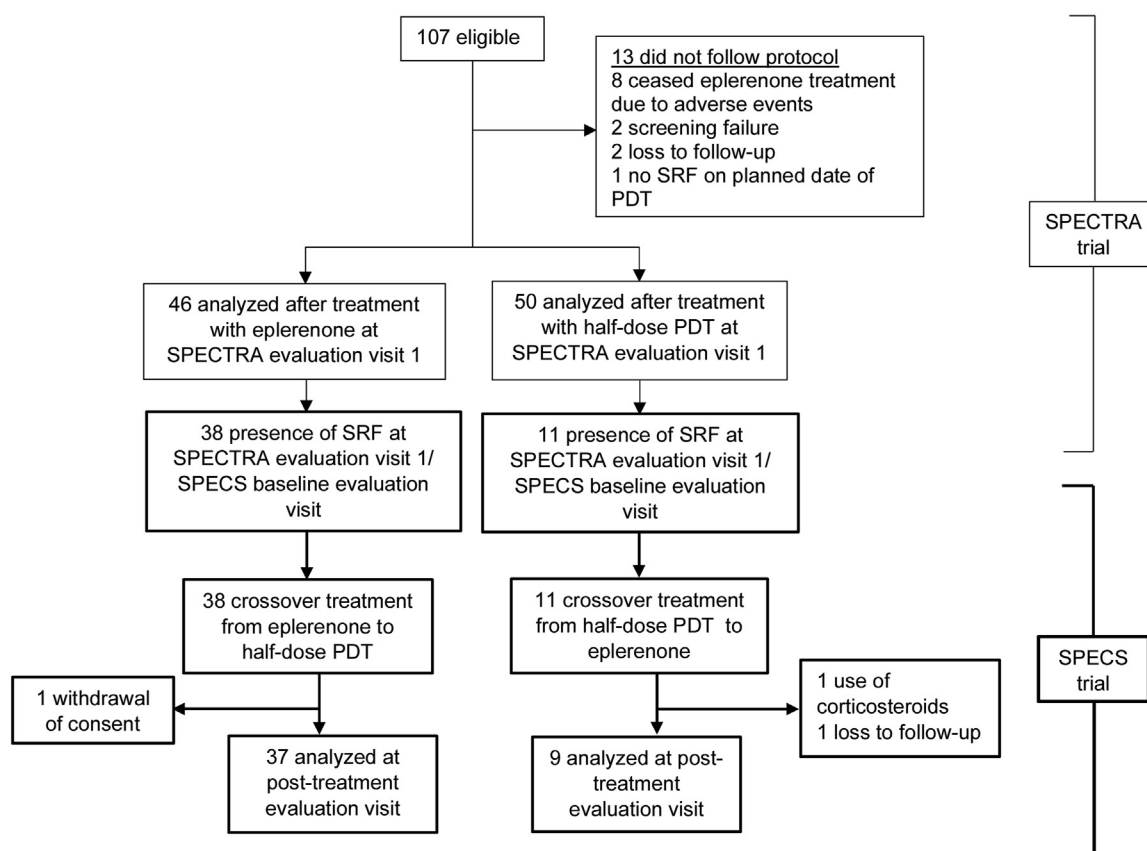


Figure 1. CONSORT flow diagram showing the patients with chronic central serous chorioretinopathy who underwent crossover treatment in the SPECS trial. PDT = photodynamic therapy; SRF = subretinal fluid; SPECS = Central Serous Chorioretinopathy Treated with Half-Dose PDT or Eplerenone Crossover Study.

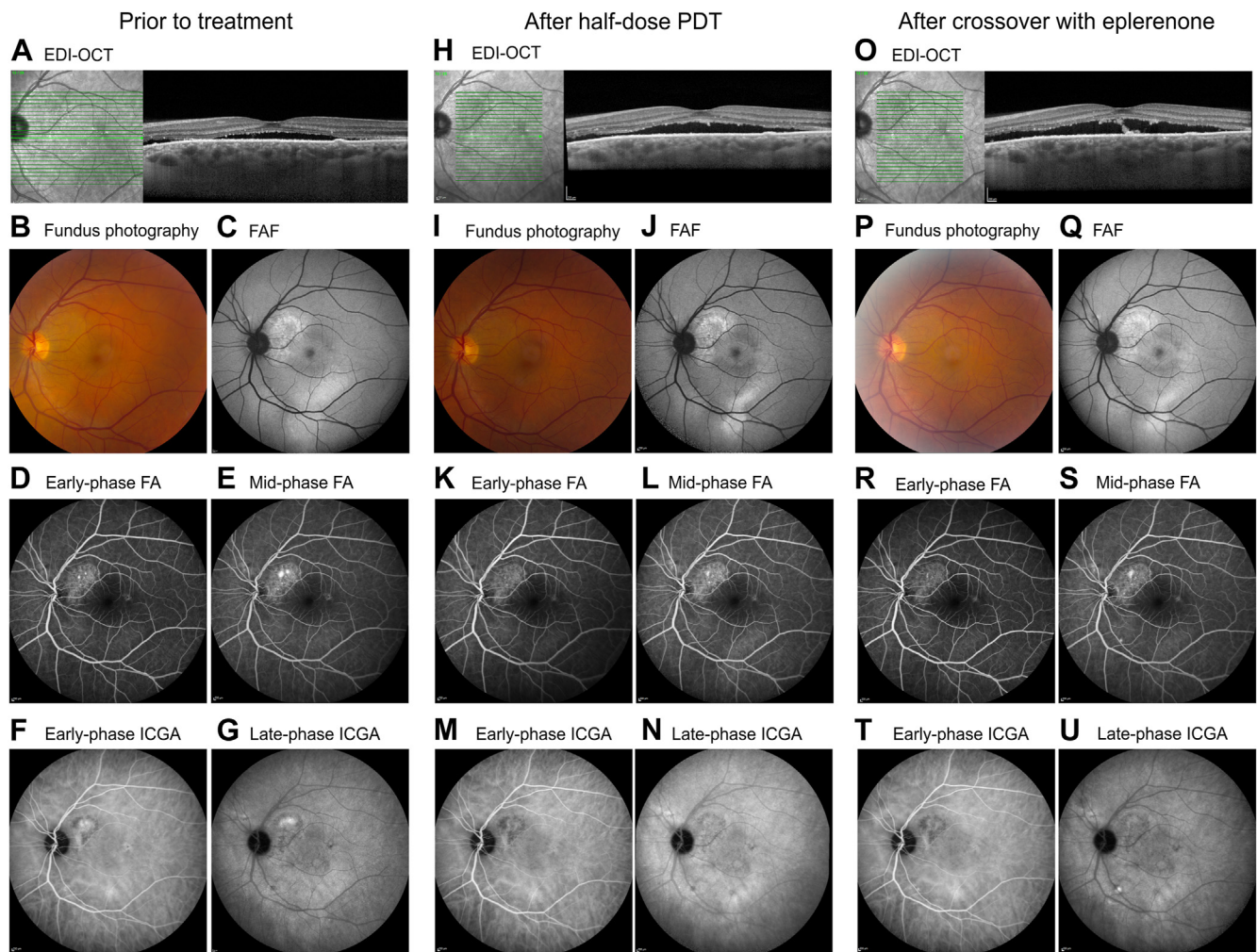


Figure 2. Multimodal imaging of a 48-year-old man with chronic central serous chorioretinopathy who received crossover treatment with half-dose photodynamic therapy after the primary failure of oral eplerenone. At the baseline visit of the SPECS trial (before crossover treatment with half-dose PDT), SRF was present on the foveal OCT (**A**). The fundus photograph (**B**) also revealed this SRF. On FAF imaging (**C**), both hyperautofluorescent and hypoautofluorescent changes could be seen. An area of focal leakage was visible on FA (**D, E**; early and midphase, respectively), whereas hyperfluorescent abnormalities typical of central serous chorioretinopathy could be detected on ICGA (**F, G**). At the posttreatment evaluation, 3 months after crossover treatment with half-dose PDT, the complete resolution of SRF on OCT had occurred (**H**); it was also visible on fundus photography (**I**). The FAF image (**J**) had not changed over time. Fluorescein angiography (**K, L**) did not show any leakage, whereas ICGA (**M, N**) showed the reduction of hyperfluorescent abnormalities. EDI-OCT = enhanced depth imaging OCT; FA = fluorescein angiography; FAF = fundus autofluorescence; ICGA = indocyanine green angiography; PDT = photodynamic therapy; SRF = subretinal fluid.

indicates that half-dose (or half-fluence) PDT can be considered to be the current treatment of choice.^{1,14–17} Thus far, it has been unknown if patients with cCSC who have previously been treated with either half-dose PDT or oral eplerenone may benefit from crossover treatment in the case of persistent SRF on OCT after the primary treatment. The current prospective study evaluates the effect of crossover treatment consisting of either eplerenone or half-dose PDT in patients with cCSC who did not achieve the complete resolution of SRF on OCT at 3 months after their original treatment with either eplerenone or half-dose PDT. We showed that the crossover from eplerenone to half-dose PDT more often led to the complete resolution of SRF on OCT compared with the crossover from half-dose PDT to eplerenone. Moreover, the crossover to half-dose PDT led to

significantly greater increases in foveal sensitivity on microperimetry and BCVA.

In this SPECS trial, the complete resolution of SRF on OCT was accomplished in 86.5% of patients after the crossover to half-dose PDT and in 22.2% of patients after the crossover to eplerenone treatment. This success rate after the crossover to half-dose PDT is similar to the outcome of the REPLACE trial, a prospective, multicenter treatment trial that studied the crossover effect of half-dose PDT in cCSC after the failure of primary high-density subthreshold micropulse laser treatment in the initial PLACE trial.^{15,16} In the REPLACE trial, the crossover to half-dose PDT after the unsuccessful high-density subthreshold micropulse laser treatment led to the complete resolution of SRF on OCT in 81% of patients.¹⁶ Moreover, the findings in the current

Table 2. Treatment Effect on Primary and Secondary End Points

Variable	Visit	Crossover from Eplerenone to Half-Dose PDT (n = 38)	Crossover from Half-Dose PDT to Eplerenone (n = 11)	P Value
Absence of SRF	Posttreatment evaluation visit	32/37 (86.5%)	2/9 (22.2%)	0.030
Odds ratio of presence of SRF	Posttreatment evaluation visit	0.0040 ($P = 0.017$)	0.0614 ($P = 0.063$)	0.030
BCVA (ETDRS letters)	Baseline evaluation visit	83.32 (n = 38, SD = 6.54)	72.18 (n = 11, SD = 14.00)	0.660
	Posttreatment evaluation visit	85.11 (n = 37, SD = 7.83)	72.91 (n = 9, SD = 14.69)	
	Difference between baseline evaluation visit and posttreatment evaluation visit	+1.80 (SD = 6.67; $P = 0.099$)	+0.73 (SD = 5.61; $P = 0.737$)	
Foveal sensitivity on microperimetry (dB)	Baseline evaluation visit	21.54 (n = 36; SD = 3.52)	21.00 (n = 9; SD = 4.20)	0.009
	Posttreatment evaluation visit	24.63 (n = 35; SD = 3.52)	20.73 (n = 9; SD = 5.17)	
	Difference between baseline evaluation visit and posttreatment visit	+3.08 (SD = 3.65; $P < 0.001$)	−0.27 (SD = 4.78; $P = 0.810$)	
Retinal sensitivity on microperimetry (dB)	Baseline evaluation visit	23.55 (n = 36, SD = 3.33)	21.76 (n = 10, SD = 4.52)	0.773
	Posttreatment evaluation visit	24.88 (n = 35, SD = 3.60)	22.74 (n = 9, SD = 5.95)	
	Difference between baseline evaluation visit and posttreatment evaluation visit	+1.33 (SD = 2.12; $P = 0.019$)	+0.98 (SD = 5.78; $P = 0.374$)	
NEI VFQ-25 score	Baseline evaluation visit	82.26 (n = 38, SD = 12.38)	81.67 (n = 11, SD = 10.68)	0.917
	Posttreatment evaluation visit	84.03 (n = 37, SD = 13.07)	82.15 (n = 9, SD = 10.20)	
	Difference between baseline evaluation visit and posttreatment evaluation visit	+1.77 (SD = 7.84; $P = 0.158$)	+1.48 (SD = 5.78; $P = 0.555$)	

BCVA = best-corrected visual acuity; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire 25; PDT = photodynamic therapy; SRF = subretinal fluid.

study are in line with the rates of complete SRF resolution that have been observed after primary half-dose PDT for cCSC in both the PLACE trial and the SPECTRA trial as well as several large retrospective studies.^{1,15,17–19} The outcome regarding the complete resolution of SRF on OCT after crossover eplerenone treatment after previous half-dose PDT in the current study (SPECS) seems similar to the rates found in the 2 previous large randomized controlled trials that studied eplerenone as a primary treatment for cCSC—the SPECTRA and VICI trials. In the SPECTRA trial, 17% of patients with cCSC treated with eplerenone achieved complete SRF resolution at 3 months. In the VICI trial, which compared oral eplerenone treatment with placebo, only 10% of the patients with cCSC in the eplerenone-treated group and 11% of the patients in the placebo-treated group had the complete resolution of SRF at 3 months after the baseline visit.¹⁴ These results showed that eplerenone was inferior to half-dose PDT in achieving complete SRF resolution and that there may be no (or a very limited) benefit of eplerenone over treatment with placebo. This is important because the complete resolution of SRF in cCSC should be the aim of treatment to reconstitute the normal anatomic and physiologic photoreceptor–RPE relationship, as previous studies have shown that the prolonged presence of SRF may lead to irreversible damage to photoreceptor cells.^{1,10,12,20,21} The question remains as to what treatment should be chosen for patients with cCSC with persistent SRF after treatment with half-dose PDT. A second PDT with reduced settings may be effective in only 32.4% of these patients after having excluded the broad

spectrum of other possible etiologies of macular SRF.^{1,15,22} However, the likelihood of complete SRF resolution after a second PDT is reduced, and such a resolution may be more likely in cases with evidence of persistent focal leakage on FA and ICGA without evidence of choroidal neovascularization.¹⁵

The secondary end points of this study included the functional parameters of BCVA, NEI VFQ-25 score, and retinal sensitivity on microperimetry. The mean foveal sensitivity on microperimetry improved significantly more in the crossover to half-dose PDT group than in the crossover to eplerenone group (+3.08 dB vs. −0.27 dB; $P = 0.009$). The mean BCVA did not increase significantly in either crossover group. The PLACE, REPLACE, and SPECTRA trials on cCSC treatment showed comparable results with regard to these functional parameters. This indicates that retinal sensitivity on microperimetry is the most sensitive functional outcome measure in cCSC, which is generally associated with relatively high baseline BCVA and NEI VFQ-25 scores.^{15,16} Indeed, it has been suggested that retinal sensitivity is a more sensitive parameter than BCVA and the NEI VFQ-25 score for detecting treatment effects in patients with CSC, which may explain the significant improvement of foveal and retinal sensitivity but not BCVA after SRF resolution in the current study.^{23,24}

The superiority of half-dose PDT over eplerenone may be attributed to the fact that half-dose PDT treats the choroid, which is presumably the primary abnormal tissue in cCSC.^{1,25–27} Photodynamic therapy has a direct treatment effect on the thickened and leaky choroid, causing choroidal

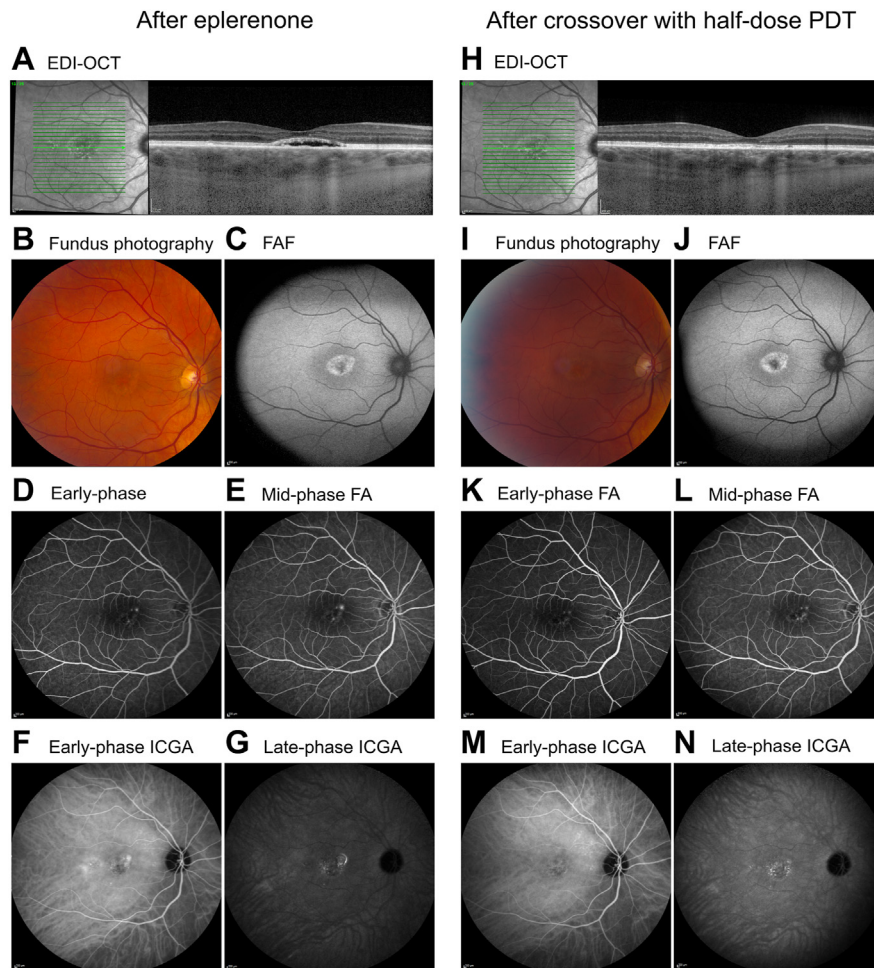


Figure 3. Multimodal imaging of a 57-year-old man with chronic central serous chorioretinopathy who received crossover treatment with oral eplerenone after the primary failure of half-dose photodynamic therapy. At the baseline visit of the SPECTRA trial (before half-dose PDT), SRF was visible on the OCT scan (A). This SRF could also be appreciated on the fundus photograph (B). The FAF image (C) revealed mainly hyperautofluorescent changes. Two “hot spots” of focal leakage were visible on FA (D, E), whereas hyperfluorescent abnormalities could be observed on ICGA (F, G), which is typical of CSC. At the SPECTRA baseline visit, 3 months after primary treatment with half-dose PDT, SRF was still present on OCT (H). The fundus photograph (I) and FAF image (J) had not changed over time. One “hot spot” of leakage was still present on FA (K, L). The hyperfluorescent changes on ICGA (M, N) had not disappeared. The OCT scan at 3 months after crossover treatment with eplerenone at the posttreatment evaluation visit (O) showed the persistence of SRF. The fundus photograph (P) and FAF image (Q) had not changed over time. One “hot spot” of leakage remained present on FA (R, S), whereas ICGA (T, U) revealed roughly stable hyperfluorescent changes. CSC = central serous chorioretinopathy; EDI-OCT = enhanced depth imaging OCT; FA = fluorescein angiography; FAF = fundus autofluorescence; ICGA = indocyanine green angiography; PDT = photodynamic therapy; SRF = subretinal fluid.

remodeling and a choroidal thickness that is closer to the normal range.²⁸ This reconstitutes the delicate balance between the damaged RPE’s outer blood–retina barrier and the choroid, with the subsequent resolution of SRF.¹ Dysfunction of the MR has been suggested to be linked to CSC in several studies, although MR antagonists, such as eplerenone, compete with other molecules for binding to this receptor. It has been proposed that excess MR activity within choroidal endothelial cells may exist in cCSC.^{2,29} However, it was recently shown that corticosteroid target gene expression in human choroidal endothelial cells could not be suppressed using MR antagonists.^{2,30} Therefore, the exact potential role of the MR in the pathogenesis of cCSC remains to be elucidated, despite the fact that we and others have shown that treatment with

the MR antagonist eplerenone does not seem to be effective for cCSC.

This trial has a few limitations. First of all, the 2 groups that received crossover treatment within this study were relatively small, particularly the crossover to half-dose PDT group. This was because of the design of the study, in which only patients who had persistent SRF at evaluation visit 1 of the SPECTRA trial could be included. Because of the fact that primary half-dose PDT within the SPECTRA trial already led to 78% of patients achieving complete SRF resolution on OCT, the remaining number of patients with persistent SRF requiring the crossover to eplerenone in the current study was small. As a result, this study was not powered a priori for the assessed end points (including the complete resolution of SRF on OCT, BCVA, retinal and foveal sensitivity on microperimetry, and

NEI VFQ-25 score). It is, therefore, striking that we still found clear, statistically significant differences in the complete resolution of SRF on OCT and foveal sensitivity on microperimetry in favor of half-dose PDT. Finally, 3 patients were lost to follow-up, which could have affected the outcome of our trial.

In conclusion, the results of this crossover trial show that patients with cCSC with a persistence of SRF after primary

treatment with oral eplerenone will benefit from a crossover treatment with half-dose PDT. Such a half-dose PDT treatment can induce a relatively fast and complete resolution of SRF on OCT in many patients, along with an improvement in foveal sensitivity on microperimetry. These findings add to the growing evidence that half-dose PDT is the treatment of choice for CSC.

Footnotes and Disclosures

Originally received: January 7, 2022.

Final revision: April 14, 2022.

Accepted: April 15, 2022.

Available online: April 22, 2022. Manuscript no. ORET-D-22-00013R2.

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Presented at The Association for Research in Vision and Ophthalmology meeting, May 7, 2021, virtual.

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The authors have made the following disclosure(s): H.M.A.F.: Support — the Blindenhulp Fellowship from Stichting Blindenhulp (The Hague, the Netherlands).

Supported by the following foundations: Stichting Macula Fonds; Retina Nederland Onderzoek Fonds; Stichting Blinden-Penning; Algemene Nederlandse Vereniging ter Voorkoming van Blindheid; Landelijke Stichting voor Blinden en Slechtzienden, which contributed through Uit-Zicht (Delft, the Netherlands); Rotterdamse Stichting Blindenbelangen (Rotterdam, the Netherlands); Stichting Leids Oogheelkundig Ondersteuningsfonds (Leiden, the Netherlands); Stichting Ooglijders (Rotterdam, the Netherlands); the Gisela Thier Fellowship of Leiden University, Leiden, the Netherlands (CB); and the Netherlands Organization for Scientific Research (VENI grant to CB).

The funding organizations had no role in the design or conduct of this research. They provided unrestricted grants.

HUMAN SUBJECTS: Human subjects were included in this study.

This study adhered to the tenets of the Declaration of Helsinki, and written informed consent was obtained from all participants. Institutional review

board/ethics committee approval was obtained from all participating centers before the start of the study.

No animal subjects were used in this study.

Author Contributions:

Conception and design: van Dijk, van Rijssen, Schlingemann, Hoyng, Boon
Data collection: Feenstra, van Dijk, van Rijssen, Diederer, Schlingemann, Hoyng, Boon

Analysis and interpretation: Feenstra, van Dijk, Tsonaka, Boon

Obtained funding: Boon; Study was performed as part of the authors' regular employment duties. No additional funding was provided.

Overall responsibility: Boon

Abbreviations and Acronyms:

BCVA = best-corrected visual acuity; **cCSC** = chronic central serous chorioretinopathy; **CSC** = central serous chorioretinopathy; **FA** = fluorescein angiography; **ICGA** = indocyanine green angiography; **MR** = mineralocorticoid receptor; **NEI VFQ-25** = National Eye Institute Visual Functioning Questionnaire 25; **PDT** = photodynamic therapy; **PLACE** = Half-Dose Photodynamic Therapy versus High-Density Subthreshold Micropulse Laser Treatment in Patients with Chronic Central Serous Chorioretinopathy; **REPLACE** = Crossover to Photodynamic Therapy or Micropulse Laser After Failure of Primary Treatment of Chronic Central Serous Chorioretinopathy; **RPE** = retinal pigment epithelium; **SPECTRA** = Half-Dose Photodynamic Therapy Versus Eplerenone: Treatment Trial for Chronic Central Serous Chorioretinopathy; **SPECS** = Central Serous Chorioretinopathy Treated with Half-Dose PDT or Eplerenone Crossover Study; **SRF** = subretinal fluid; **VICI** = Eplerenone for Chronic Central Serous Chorioretinopathy in Patients with Active, Previously Untreated Disease for More than 4 Months.

Keywords:

Central serous chorioretinopathy, Eplerenone, Half-dose photodynamic therapy, Mineralocorticoid receptor agonist.

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