## The spectrum of central serous chorioretinopathy: clinical characteristics, genetic associations and outcome of treatment

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# Chapter 4

# Efficacy of photodynamic therapy in CSC

# Efficacy of photodynamic therapy in steroid-associated chronic central serous chorioretinopathy: a case–control study

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## ABSTRACT

Purpose: To investigate whether patients who developed chronic central serous chorioretinopathy (cCSC) in association with corticosteroid treatment respond differently to photodynamic therapy (PDT) as compared to patients who have not used corticosteroids.

Methods: Clinical evaluation included visual acuity (VA), fundoscopy, optical coherence tomography (OCT), fluorescein and indocyanine green angiography. The main outcome measure was a complete resolution of subretinal fluid (SRF) on OCT after PDT.

Results: One hundred and twenty-three eyes (117 patients), including 35 steroid associated cases (29%), who received PDT treatment with reduced settings for active cCSC were included. Complete resolution of SRF on OCT was seen in 69% of the steroid-associated cases and in 50% of the controls after PDT treatment ($p = 0.062$). At the final follow-up moment, 74% of the cases had a complete resolution of SRF compared to 60% in the control group ($p = 0.142$). The VA at the first visit after therapy showed an increase in both groups (mean VA before treatment; cases: 69±14 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, controls: 74±13 ETDRS letters, mean VA first visit after treatment; cases: 76±13 ETDRS letters, controls: 75±13 ETDRS letters). No significant differences were seen in response to PDT between the patients who continued corticosteroid treatment and those who ceased the use of corticosteroids.

Conclusions: Photodynamic therapy appears to be equally effective in patients suffering from steroid-associated cCSC as compared to patients with cCSC who do not use corticosteroids. Continuation of corticosteroids at the time of PDT treatment does not seem to adversely affect PDT response.

## INTRODUCTION

Central serous chorioretinopathy (CSC) is a relatively common early onset eye disease, characterized by an accumulation of leaked serous fluid under the retina, causing a detachment of the neuroretina. This subretinal fluid (SRF) leakage results from dysfunction of the retinal pigment epithelium (RPE), presumably caused by choroidal congestion and thickening and hyperpermeability of the choroid.[1-4]

Two main subtypes can be distinguished: acute CSC and chronic CSC (cCSC).[1-8] In acute CSC, patients manifest with sudden and marked vision loss, and acute CSC is characterized by a focal leakage spot seen on fluorescein angiography (FA) that indicates leakage at the level of the retinal pigment epithelium (RPE).[1-10] In most patients with acute CSC, this SRF resolves spontaneously within 3 months with near-complete visual recovery.[2, 4]

Compared to patients with acute CSC, patients with cCSC present at an older age, with a disease onset that is generally experienced as less sudden.[7, 8] Furthermore, cCSC generally shows a more diffuse and sometimes multifocal leakage pattern on FA and especially on indocyanine green angiography (ICGA), often with more widespread and irregular RPE changes associated with various degrees of low-grade leakage as compared to acute CSC.[1-11] In contrast to acute CSC, the SRF accumulation in cCSC tends to persist for more than 3 months, although it can wax and wane multiple times.[4-6] Additionally, ICGA characteristically demonstrates widespread hyperfluorescent areas of choroidal congestion and hyperpermeability, which are more extensive in cCSC than in acute CSC.[1, 9, 12-14] These abnormalities mostly overlap with those seen on FA, but can also be present without any evidence of leakage on FA in cCSC.[9]

A persistent serous neuroretinal detachment in cCSC can cause progressive and irreversible photoreceptor damage.[1, 15, 16] Therefore, it is common practice to treat these patients, although prospective multicenter randomized controlled trials on the optimal treatment are largely lacking. Currently, photodynamic laser therapy (PDT) is one of the most frequently used treatment modalities in cCSC, with reported anatomical success rates in retrospective studies ranging from 70–100%.[17-20] This is a relatively broad range. Therefore, it is of clinical relevance to identify possible factors that could influence treatment success.

Although the exact mechanism by which CSC develops is largely unclear, several associations and risk factors have been described in the literature, such as male gender, stress, type A personality, pregnancy and the use of corticosteroids.[21-23] In addition, genetic risk factors have recently been identified in CSC.[24-26] In particular, the use of corticosteroids is one of the most prominent risk factors known in CSC, although the reported effect sizes vary (odds ratio: 2.4 and 10.3).[23, 27] Some patients report a clear association between the initiation of corticosteroids and the start of CSC-associated visual complaints. This could indicate possible differences in the disease mechanisms between steroid users and non-

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steroid users. The previous or ongoing use of corticosteroids is likewise thought to be a risk factor for ongoing disease activity in cCSC and could potentially limit the efficacy of treatment.

In studies on PDT as treatment for cCSC, the use of corticosteroids is often an exclusion criterion; therefore, it is unclear whether the outcome of PDT in cCSC is different compared to patients who have no history of current or previous corticosteroid use.

The aim of this study was to investigate whether the response to PDT is different in treatment-naive patients presenting with steroid-associated cCSC versus cCSC patients without a history of steroid use.

## PATIENTS AND METHODS

### *Patients*

The patients enrolled for this retrospective case–control study were seen at the outpatient clinics of the Departments of Ophthalmology of the Radboud University Medical Center (Nijmegen, the Netherlands) and the Leiden University Medical Center (Leiden, the Netherlands) between January 2004 and February 2015. We retrospectively reviewed the medical records of all patients who had been diagnosed with cCSC and who consequently had been treated with PDT as first-line therapy. The diagnosis of cCSC was based on characteristic features as seen on multimodal imaging consisting of optical coherence tomography (OCT), FA and ICGA. These features included presence of SRF in the macula on OCT, and irregular diffuse and/or multifocal hyperfluorescent areas in the posterior pole, corresponding to irregular RPE window defects with or without obvious hot spots of leakage on FA, with one or more corresponding hyperfluorescent areas on ICGA (Fig. 1).[26] Approval for this study was obtained at the local institutional review boards, and the study adhered to the tenets of the Declaration of Helsinki.
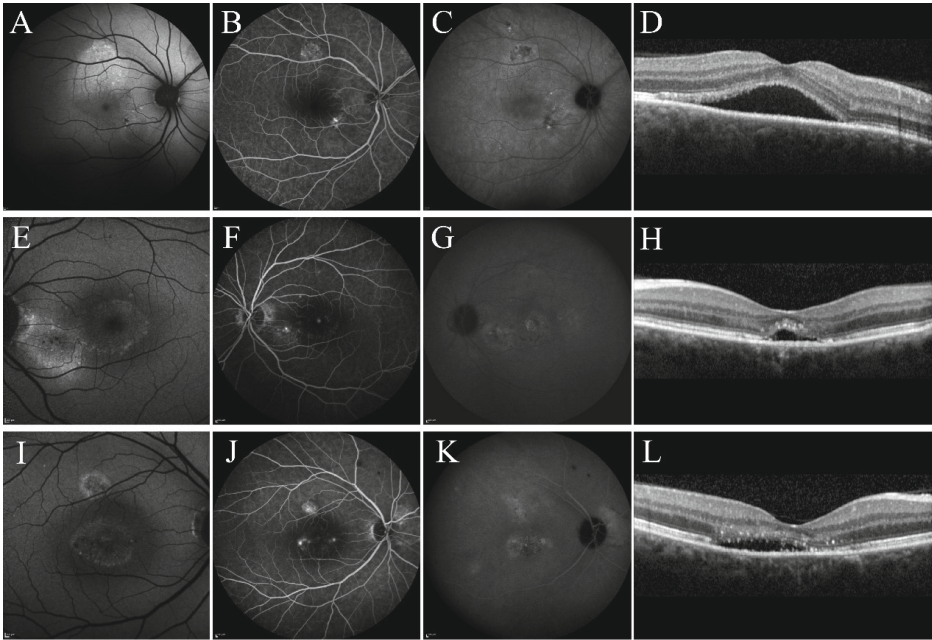
**Figure 1.** Examples of the typical abnormalities as observed on multimodal imaging techniques [left to right; fundus autofluorescence (FAF), early fluorescein angiography (FA), mid-phase indocyanine green angiography (ICGA) and optical coherence tomography (OCT)] in three patients with chronic central serous chorioretinopathy (cCSC). The images in the upper two rows belong to two patients with steroid-associated cCSC. (A–D) The right eye of a 45-year-old male bodybuilder with frequent steroid injections, illustrating juxtafoveal hyperautofluorescent irregularities of the retinal pigment epithelium (RPE) layer on FAF(A), multifocal leakage on FA and ICGA (B-C), and subfoveal subretinal fluid (SRF) on OCT(D). (E–H) The left eye of a 48-year-old male who used topical steroid cream for skin problems. The FAF shows hyperautofluorescence inferotemporal of the optic disc (E), and hot spots indicating leakage are seen on FA and ICGA accompanied by SRF on OCT (F–H). (I–L) The right eye of 56-year-old male who did not report the use of corticosteroids. FAF shows central hyperautofluorescence corresponding to hyperfluorescent leakage on FA and ICGA (I–K), and a flat SRF accumulation on OCT(L).

At the visit prior to the PDT, at the first evaluation visit after therapy and at the last available follow-up visit, the following parameters were collected: visual acuity (VA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters, start date of visual symptoms, the use of corticosteroids (including reason for use and route of administration), presence of SRF on OCT and central retinal thickness (CRT) as measured automatically by the integrated software of the Spectralis TM RA+OCT (Heidelberg Engineering, Heidelberg, Germany). Due to a satisfying response to treatment, only the first evaluation visit was available in a part of the cases and controls. If the first evaluation visit after treatment was also the last available follow-up visit, the collected information was only used in the analysis for the first evaluation visit. An exception was made for the absence of SRF at final follow-up.

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### *Steroid use*

Patients were divided into two groups based on their reported use of corticosteroids: patients who used corticosteroids within 12 months prior to the development of the cCSC (cases) and patients who did not have a history of current or prior use of any type of corticosteroids controls). For the first group, only patients in whom a relation between steroid use and the onset of CSC symptoms was highly suspected were included. This probability of a causal relationship was assessed by the treating physician at the moment of diagnosis.

For subanalysis in the cases, a further distinction was made between patients who continued steroid use in the period when PDT had been performed and those who ceased corticosteroid use before treatment.

### *Photodynamic therapy*

For this study, PDT treatment was performed with reduced settings, either with half-dose or half-time as compared to the original settings described for neovascular age-related macular degeneration, depending on the preference of the treating physician (Liu et al. 2014; Tsai & Hsieh 2014). Before treatment, the pupils were dilated (with 1.0% tropicamide and 2.5% phenylephrine). Verteporfin [Visudyne ®; 3 mg/m2 (for the half-dose PDT) and 6 mg/m2 (for the half-time PDT)] was intravenously administered, with an infusion time of 10 min. At 15 min after the start of the infusion, an anesthetic eye drop was applied (oxybuprocaine 0.4% or equivalent), a contact lens (Volk® PDT lens) was positioned on the affected eye, and a laser beam was focused on the area to treat of which the spot size was based on hyperfluorescence as seen on mid-phase (approximately 10 min) ICGA. The PDT was performed with standard 50 J/cm2 fluency, a PDT laser wavelength of 689 nm and a treatment duration of 83 seconds in patients treated with half-dose PDT and 42 seconds in the half-time PDT.

### Definition of the outcomes

Effectiveness of the PDT was based on the anatomical recovery as seen on OCT, defined as a complete absence of SRF. Furthermore, we compared the VA and the CRT before and after treatment in each patient and between the (sub)groups. Additionally, we analyzed the period of time needed to achieve a complete resolution of SRF between the cases and controls. To evaluate the effectiveness of PDT over time, we analyzed the number of recurrences and also the number of additional treatments that each patient received until the end of the study.

### Statistical analysis

Statistical analyses were performed using IBM SPSS software for Windows version 20. For comparisons of continuous numerical data in demographic characteristics and study outcome measures, we performed a dependent t-test, an independent t-test or a Mann–Whitney U-test as appropriate. Categorical data were analyzed using a chi-square test.

Furthermore, two survival analyses were performed and Kaplan–Meier survival plots were generated comparing the cases with the controls. The following events were used: 'complete resolution of SRF after one PDT treatment' and 'complete resolution of SRF at final follow-up'. A two-sided p-value of less than 0.05 was considered statistically significant.

## RESULTS

### Patient characteristics

#### Demographics
Thirty-five eyes of 33 patients (mean age at time of PDT treatment: 55 ± 11.7 years) with corticosteroid-associated cCSC and 88 eyes of 84 patients (mean age at time of PDT treatment: 52 ± 11.1 years) who did not report any use of corticosteroids were included in this study (Table 1). General characteristics including age, gender, reported duration of complaints, elapsed time between treatment and first control visit, baseline VA and mean CRT as measured on OCT at baseline did not differ significantly between the steroid users and the non-steroid users (Table 1).

**Table 1** Patient demographics in cases and controls

|  | Cases | Controls | P |
|---|---|---|---|
| Eyes (patients) | 35 (33) | 88 (84) | Not applicable |
| Gender (m/f) | 24/ 11 | 72 / 16 | 0.109 |
| Age [a] [range] in years | 54.6 [31-80] | 52.0 [29-81] | 0.285 |
| VA pre-therapy in ETDRS letters (SD) | 69 (14) | 74 (13) | 0.065 |
| CRT before therapy (SD) | 381.3μm (111) | 374.9μm (116) | 0.782 |
| Duration of complaints in weeks [b] [range] | 38.8 [3.1-706.9] | 30.3 [3.7-566.0] | 0.445 |
| Half-dose PDT / Half-time PDT | 30 / 5 | 82 / 6 | 0.190 |

[a] Age at the time of photodynamic therapy treatment
[b] Median number of weeks between the start of the complaints and therapeutic intervention
ETDRS; Early Treatment Diabetic Retinopathy Study, PDT; Photodynamic Therapy, SD; Standard Deviation, VA; Visual Acuity

Among the 33 patients with reported (previous) use of corticosteroids, nine patients (27%) used corticosteroid cream, nine patients (27%) reported nasal spray containing corticosteroids, seven patients (21%) used oral corticosteroids, four patients (12%) used corticosteroids by an inhaler, one patient (3%) received illegal corticosteroid injections for professional bodybuilding, and the remaining hree patients (9%) reported (previous) use of corticosteroids via more than one way of administration.

The corticosteroid use was continued before, during and after PDT treatment in 16 of 35 eyes (46%).

**Optical coherence tomography**
At the first control visit after PDT (on average 7.4 ± 2.8 weeks after treatment in the cases, and 7.9 ± 2.9 weeks after treatment in the controls), 22 eyes (63%) of the patients with steroid associated cCSC and 40 eyes (45%) of the controls showed a complete absence of SRF on OCT. Moreover, a clear reduction in SRF was seen in 26% (n = 9) of the steroid-associated patients and in 28% (n = 25) of the non-steroid associated controls. During follow-up, this reduction led to a complete absence of SRF in two of these cases (22%) and in four eyes (16%) of these controls. In three of 35 steroid-associated eyes (9%) with cCSC, and 17 of the 88 eyes (19%) of controls with cCSC, no changes in SRF were observed on OCT at the first control visit. One eye with steroid associated cCSC (3%) and six eyes (7%) in the control group showed an increase in SRF.

When comparing the resolution of SRF using a survival analysis, there was a trend for subjects in the corticosteroid associated cCSC group to have a faster complete resolution of SRF as compared to the controls (Fig. 2). A reduction in CRT was seen in both groups at the first and final follow-up after treatment (Table 2). There was no significant difference in the mean reduction in CRT between both groups at final follow-up [steroid users (n = 21); 114.1 ± 143.9 µm, non-steroid users (n = 46); 109.4 ± 109.7 µm, $p$ = 0.883, independent t-test].

**Table 2** Comparison of variables of interest at visit pre- and post-photodynamic therapy in cases and controls

|  | Cases | Controls | P |
|---|---|---|---|
| CRT pre-therapy in µm (SD) | 381.1 (111) (n=35) | 374.9 (116) (n=88) | 0.782 |
| CRT at first follow-up[a] in µm (SD) | 290.9 (121) (n=35) | 282.4 (81) (n=88) | 0.655 |
| CRT at final follow-up[b] in µm (SD) | 289.4 (114) (n=21) | 261.7 (54) (n=46) | 0.298 |
| VA pre-therapy in ETDRS letters (SD) | 69 (14) (n=35) | 74 (13) (n=88) | 0.065 |
| VA at first follow-up in ETDRS letters [a] (SD) | 76 (13) (n=35) | 75 (13) (n=88) | 0.499 |
| VA at final follow-up in ETDRS letters [b] (SD) | 72 (18) (n=21) | 71 (14) (n=45) | 0.943 |

[a] Average number of weeks between therapeutic intervention and first follow-up in the steroid group: 7.4 weeks, in the non-steroid group: 7.9 weeks (p= 0.445)
[b] Average number of weeks between therapeutic intervention and final follow-up in the steroid group: 48.4 weeks, in the non-steroid group: 49.6 weeks (p= 0.886)
CRT; Central Retinal Thickness, ETDRS; Early Treatment of Diabetic Retinopathy Study, SD: Standard Deviation, VA; Visual Acuity

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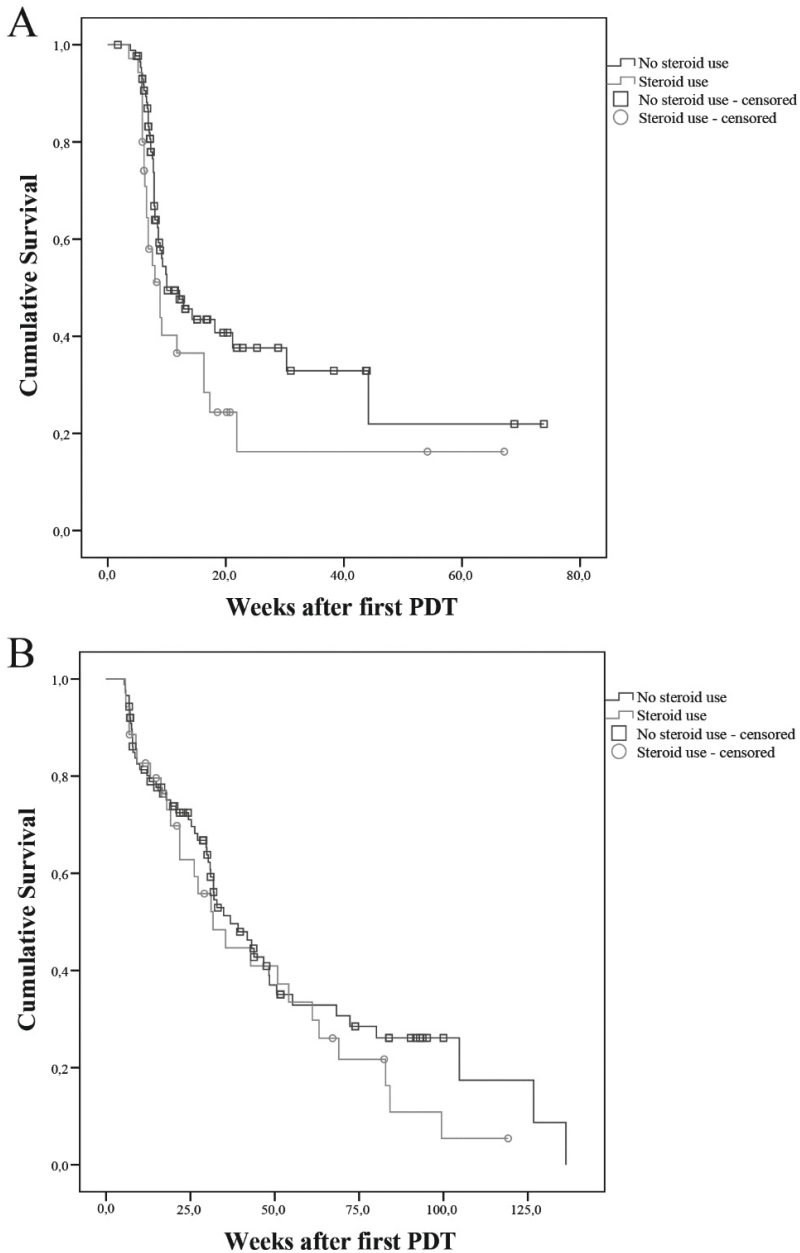
**Figure 2.** Kaplan–Meier curves showing the cumulative fraction in treated patients with chronic central serous chorioretinopathy. A. End-point: 'Full resolution of subretinal fluid (SRF) after 1 photodynamic therapy'; median duration before SRF fully resolved in cases: 8.9 weeks [95% CI: 6.4–11.3] and controls: 10.0 weeks [95% CI: 5.2–14.8] ($p$ = 0.064). B. End-point: 'Complete resolution of SRF at final follow-up'; median duration before SRF fully resolved in cases: 31.7 weeks [95% CI: 18.6–44.8] and controls: 36.8 weeks [95% CI: 25.5–48.2] ($p$ = 0.344). PDT= photodynamic therapy.

During follow-up, a recurrence of SRF on OCT was seen in six of the 24 patients (25%) with steroid-associated cCSC and in nine of the 44 patients (20%) with non-steroid-associated cCSC who initially showed a good response (absence of SRF on OCT) after PDT.

At the final visit (on average 48.4 ± 31.4 weeks post-therapy in cases, and 49.6 ± 49.7 weeks posttherapy in controls), SRF had completely resolved in 26 of 35 eyes (74%) with steroid-associated cCSC, of which five eyes (19%) had received additional treatments that consisted of either a second PDT, conventional laser therapy of the hot spot, high-density subthreshold micropulse laser treatment, intravitreal bevacizumab or a combination of the aforementioned treatments [mean number of additional treatments; 1.8 (range 1–3)]. In the control group, 53 eyes (60%) had complete absence of SRF at final follow-up. Of these eyes, 18 eyes (34%) received additional treatment consisting of either a second PDT treatment, high-density subthreshold micropulse laser treatment, intravitreal bevacizumab, intravitreal aflibercept or a combination of the aforementioned treatments [mean number of additional treatments; 1.7 (range 1–4)].

Of the eyes with SRF on OCT at the last available visit [nine eyes (26%) in the steroid-associated cases and 35 eyes (40%) in the controls], 18 eyes received additional treatment [two eyes (22%) in the cases and 16 eyes (46%) in the controls].

**Patients with suspected neovascularization**
In both groups, a subretinal choroidal neovascularization (CNV) was suspected during follow-up in three eyes (9%) in the steroid-associated cCSC group, and four eyes (5%) in the controls, for which intravitreal antivascular growth factor treatment (anti- VEGF) was initiated. One of these patients initially responded well to the first PDT treatment with absence of SRF on OCT, followed by recurrence of the SRF. After anti-VEGF therapy, two eyes (29%) had complete resolution of SRF, and five eyes (71%) had persistent SRF. Re-evaluation of the baseline imaging showed small lesions on OCT, FA or ICGA that retrospectively could indicate a subtle pre-existent occult CNV or a small polypoidal choroidal vasculopathy (PCV) at baseline in four eyes (57%). The mean age of the seven patients suspected to have a CNV or PCV during follow-up was 64 years, which was significantly older as compared to the general group (mean age; 52 years, $p = 0.006$, independent t-test). None of these patients had evidence of drusen on ophthalmoscopy, OCT and FA.

**Visual acuity**
The mean VA increased significantly after PDT treatment in the steroid associated cCSC group when comparing the VA pre-PDT (69 ± 14 ETDRS letters) to the VA at the first control visit after treatment (76 ± 13 ETDRS letters, $p < 0.001$, independent t-test). This was also the case in the nonsteroid-associated patient group (VA before treatment; 74 ± 13 ETDRS letters, VA after treatment; 75 ± 13 ETDRS letters, $p = 0.014$, independent t-test).

At the last available visit, the mean VA was comparable between cases [72 ± 18 ETDRS letters (n = 21)] and controls [71 ± 14 ETDRS letters (n = 45)] (Table 2). Of those patients in the case group who showed a complete resolution of SRF (n = 24), the VA had improved significantly after the PDT (VA pre-PDT: 70 ± 15 ETDRS letters; VA post-PDT: 78 ± 13 ETDRS letters, *p* = 0.001). This was also the case in control eyes with a complete SRF resolution (n = 44) after the PDT (VA pre-PDT: 72 ± 15 ETDRS letters; VA post-PDT: 78± 13 ETDRS letters, *p* = 0.001).

No significant differences were found in treatment response on OCT and visual outcome when dividing the group of steroid users into a group of patients who continued the use of corticosteroids (oral, cutaneous creme, nasal spray, inhaler or a combination) during the study period (46% of 35 cases) and a group of patients who stopped the use of corticosteroids during therapy (54%) (Table 3). In particular, of the six eyes of five patients who continued the use of oral corticosteroids during the PDT treatment, four eyes (67%) showed a complete resolution of SRF on OCT after PDT treatment at last available visit.

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**Table 3** Comparison of central retinal thickness and visual acuity between patients who continued corticosteroid use during photodynamic therapy (PDT) and those who ceased corticosteroid treatment before PDT.

|  | **Steroids were continued** | **Steroids were ceased** | **P** |
|---|---|---|---|
| CRT pre-therapy in μm (SD) | 405.0 (98) (n=16) | 361.0 (119) (n=19) | 0.249 |
| CRT at first follow-up [a] (SD) | 286.3 (103) (n=16) | 294.7 (137) (n=19) | 0.841 |
| CRT at final follow-up [b] (SD) | 227.9 (107) (n=11) | 203.1 (125) (n=10) | 0.638 |
| VA pre-therapy in ETDRS letters (SD) | 66 (14) (n=16) | 71 (14) (n=19) | 0.285 |
| VA at first follow-up in ETDRS letters [a] (SD) | 74 (14) (n=16) | 78 (11) (n=19) | 0.272 |
| VA at final follow-up in ETDRS letters [b] (SD) | 69 (23) (n=11) | 75 (12) (n=10) | 0.434 |

[a] Average number of weeks between therapeutic intervention and first follow-up in patients who continued corticosteroid treatment: 8.0 weeks, in patients who stopped corticosteroids: 6.9 weeks (p=0.265)

[b] Average number of weeks between therapeutic intervention and final follow-up in patients who continued corticosteroid treatment: 23.6 weeks, in patients who stopped corticosteroids: 21.7 weeks (p=0.801)

CRT;Central Retinal Thickness, ETDRS; Early Treatment of Diabetic Retinopathy Study, SD; Standard Deviation, VA; Visual Acuity

## DISCUSSION

This study suggests that the current or recent use of corticosteroids in cCSC does not adversely affect the response to PDT. No significant differences were seen between the corticosteroid-associated cCSC cases and the controls regarding the treatment response on OCT and on visual outcome.

Current literature reports an improvement of retinal anatomy and VA in 70–100% of cCSC after PDT treatment.[17-20, 28, 29] The success rate of PDT treatment, defined as a complete absence of SRF on OCT, found in the present study is lower than reported in previous studies. A possible explanation could be that our study evaluated a phenotypically different patient group. Previous studies have differentiated acute and chronic CSC either based on the duration of presence of SRF or based on phenotypic characteristics. However, thus far no consensus exists on how to define chronicity in CSC.[3, 30] Where some authors consider duration of presence of SRF up to 2– 3 months as typical for acute CSC,[1, 9-11, 30] which implicates that if the SRF accumulation would exist longer than 3 months one can speak of a cCSC, others argue that CSC becomes chronic after a duration of more than 6 months.[31, 32] Also, division based on the extensity of abnormalities as seen on multimodal imaging has been described, and Wang et al. demonstrated that in case of a subretinal detachment of more than 4 months, irreversible atrophy in the macula may already ensue.[15] Therefore, in the current study, patients with cCSC were included not only based on a disease duration of more than 3 months, but also on the presence of features indicative of chronicity on multimodal imaging: presence of SRF in the macula on OCT, and irregular diffuse and/or multifocal hyperfluorescent areas in the posterior pole, corresponding to irregular RPE window defects with or without obvious hot spots of leakage on FA, with one or more corresponding hyperfluorescent areas on ICGA.[26] In contrast to acute CSC, patients with cCSC have (and often present with) more widespread abnormalities on multimodal imaging.[1, 9, 12-14] Although the current study included cases who seemed to have a follow-up less than 3 months before receiving an intervention, all patients presented phenotypic features that confirmed chronicity. It is likely that the short follow-up time was caused by lack of information about the exact moment of onset of symptoms.

In our study, no differences were found in efficacy of PDT in patients with cCSC who ceased the corticosteroids in comparison with the patients who continued corticosteroids. Lee et al. previously found a treatment response with absence of SRF in 100% of the cases, using either full dose or half-time PDT, in a retrospective study of nine patients with steroid associated CSC.[33] In this study, five of the nine patients discontinued the steroid use, which could be of influence on the response.[33] The findings in our study are encouraging as they suggest that the continuation of corticosteroid treatment, if inevitable for other medical indications, does not preclude a favorable response to PDT. It is unclear through which pathophysiological mechanisms corticosteroid use is associated with cCSC. For instance, it is still unknown whether corticosteroids are required to develop cCSC in

the first place or whether the use of corticosteroids is merely an additional trigger for a subclinical disease state that is already present. The use of corticosteroids is postulated to induce platelet aggregation and vasoconstriction and to suppress vasodilators (e.g. nitric oxide and prostaglandins).[22, 27, 34] Consequently, this may lead to microthrombus formation, which may alter choroidal perfusion and vascular permeability.[22, 27, 34] On the other hand, corticosteroids do not have the same effect in every patient; Han et al., for example, demonstrated that the choroidal thickening seen in steroid-induced CSC seems to be more an exceptional rather than a dose-dependent response that may be selectively present in vulnerable individuals.[35] Choroidal congestion and hyperpermeability appear to be present in patients with cCSC using corticosteroids as well as in those who do not. Photodynamic therapy (PDT) may be an effective treatment in both patient subgroups as it is presumed to induce a remodeling of the choroidal vasculature, supposedly through selective vascular occlusion due to damage to choroidal endothelial cells and subsequent thrombotic events of the choriocapillaris that cause a decrease in choroidal thickness, a reduction in choroidal vascular hyperpermeability and leakage through the RPE, and a restoration in the fluid balance in the subretinal space.[36, 37] Photodynamic therapy (PDT) using standard settings (verteporfin dose of 6 mg/m2, fluency of 50 J/cm2, treatment time of 830 seconds) has been associated with adverse effects such as choroidal ischemia, RPE atrophy and CNV formation,[4, 17, 38-40] although a 4-year follow-up study in cCSC has not found any adverse effects using this treatment in 46 eyes with cCSC.[41] Photodynamic therapy (PDT) using reduced settings has commonly been adopted as this strategy appears to be equally effective and potentially safer compared to standard settings.[4, 17, 40, 42, 43] However, retrospective evaluation of the baseline imaging in our study showed that of seven patients who were suspected to have a CNV or PCV during follow-up, four patients had small lesions that were suspect for CNV or PCV. These lesions, however, were very subtle and easily overlooked even by experienced ophthalmologists. In the remaining three patients, who had no suspect lesions at baseline, it remains unclear whether the PDT with reduced settings may have triggered further growth of a possible concealed small CNV. This would indicate that the CNV or the PCV could have been primarily associated with CSC-like changes before PDT was performed, as reported previously.[44, 45] Therefore, patients with cCSC should be monitored closely for possible occult CNV and/or PCV, especially elderly patient with a cCSC phenotype, and in case of non-response to PDT, the initial diagnosis should be reevaluated.

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In conclusion, this study shows that PDT is an effective treatment in patients suffering from steroid-associated cCSC, and suggests that the efficacy is comparable to PDT in patients with cCSC who do not use corticosteroids. Although the pathophysiological mechanism may not be identical in both patient groups, it is not reflected in the overall treatment outcome of PDT. Therefore, PDT can also be offered as a treatment strategy in patients who are (or previously have been) on corticosteroid treatment.

**Acknowledgments**

An abstract of this article has been presented on the annual meeting of The Association for Research in Vision and Ophthalmology on May 3rd - 7th 2015.

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