Central Serous Chorioretinopathy: Long-Term Results After Photodynamic Therapy

Coriorretinopatia Serosa Central: Resultados a Longo Prazo Após Terapia Fotodinâmica

Pedro Nuno Pereira[1,2], Sofia Catalão Ferreira[3], Mário Soares[1], Pedro Melo[1], Cláudia Farinha[1,2,3,4,5], João Pedro Marques[1,2,3,4,5], Isabel Pires[1,2,3,4,5], Maria da Luz Cachulo[1,2,3,4,5], Joaquim Murta[1,2,3,4,5], Rufino Silva[1,2,3,4,5]

[1] Ophthalmology Department, Centro Hospitalar e Universitário de Coimbra (CHUC), Coimbra, Portugal;
[2] Association for Innovation and Biomedical Research on Light and Image (AIBILI), Coimbra, Portugal;
[3] University of Coimbra, Coimbra Institute for Clinical and Biomedical Research, Faculty of Medicine (iCBR-FMUC), Coimbra, Portugal
[4] University of Coimbra, Center for Innovative Biomedicine and Biotechnology (CIBB), Coimbra, Portugal
[5] Clinical Academic Center of Coimbra (CACC), Coimbra, Portugal

Recebido/Received: 2021-11-24 | **Aceite/Accepted:** 2021-12-06 | **Publicado/Published:** 2021-12-31

DOI: https://doi.org/10.48560/rspo.25892

ABSTRACT

INTRODUCTION: Central serous chorioretinopathy (CSC) is an idiopathic syndrome characterized by neurosensory detachments of the retina. Development of chronic CSC is an indication to treat, and ICGA-guided verteporfin photodynamic therapy has been shown to be very effective.

Our objective was to evaluate the 13-year follow-up of chronic CSC patients treated with standard-fluence PDT and to explore the long-term microstructural and vascular choroidal changes related to the disease and treatment.

METHODS: Retrospective, interventional case-series analysis was conducted on 18 patients with cCSC, treated with standard PDT. Evaluations were performed every 3 months in the first year, every 6 months during the second year, and annually thereafter. All participants underwent a comprehensive ophthalmic examination. Retinal and choroidal imaging was performed with SD-OCT, SS-OCT, Optomap and OCTA.

RESULTS: Twenty-three eyes of eighteen patients were included, with a mean age of 63.9±8.5 years. The mean follow-up was 15.8±1.4 years. The mean number of sPDT treatments was 1.2±0.4. At baseline, subretinal fluid was found in all eyes, RPE proliferation in 9.1% and atrophy in 9.1% of the eyes. There was not a statistically significant improvement in BCVA, despite an initial mean gain of 5.08±10.36 letters at month 12 ($p<0.05$), which decreased to 1.87±11.9 letters at the end of follow-up. In the final visit, only 3 eyes present subretinal fluid, 3 had fibrosis, but 15 (65.2%) showed atrophy. Central macular thickness reduced from 340.7±114.9 μm to 228.7±38.6 μm at end of the follow-up. The choroid of treated eyes was thicker but the choriocapillaris had less vascular flow compared to fellow-nontreated eyes at this point. Only one session of sPDT was needed in the 19 eyes, and 4 underwent 2 sessions.

CONCLUSION: ICGA-guided PDT full-fluence is a safe procedure, with no ocular or systemic adverse effects registered in our cohort. After 13 years, only 17.4% required 2 sessions. However, two-thirds of the cases presented atrophy in the last visit, which is probably related to the degenerative course of the disease and limited the initial visual acuity gains in the long term.

KEYWORDS: Central Serous Chorioretinopathy/drug therapy; Photochemotherapy; Verteporfin/therapeutic use.

RESUMO

INTRODUÇÃO: A coriorretinopatia serosa central (CSC) é uma síndrome idiopática caracterizada por descolamentos serosos da retina. O desenvolvimento de CSC crónica é uma indicação para tratamento e a terapia fotodinâmica com verteporfina guiada por ICGA tem-se revelado muito eficaz.

O nosso objectivo foi avaliar a eficácia e segurança da TFD *standard* com verteporfina, durante um período de seguimento de 13 anos, descrevendo as alterações microestruturais e vasculares a longo prazo.

MÉTODOS: Procedeu-se a um estudo retrospetivo de doentes com CSC crónica, tratados com TFD *standard*. As avaliações periódicas foram realizadas a cada 3 meses no primeiro ano, cada 6 meses no segundo e, posteriormente, anualmente. Todos os participantes realizaram um exame oftalmológico completo. A imagiologia da retina e da coróide foi obtida recorrendo a abordagem multimodal com SD-OCT, SS-OCT, Optomap e OCTA.

RESULTADOS: Foram incluídos 23 olhos de 18 doentes, com uma idade média de 63,9±8,5 anos. O período médio de *follow-up* foi 15,8±1,4 anos. O número médio de tratamentos de TFDs foi de 1,2±1,4. No início do estudo, o fluído subretiniano estava presente em todos os olhos, a proliferação do EPR em 9,1% e atrofia em 9,1% dos olhos. Não se observou melhoria estatisticamente significativa na MAVC, apesar de um ganho médio inicial de 5,08±10,36 letras no 12º mês (p<0,05), que diminuiu para 1,87±11,9 letras no final do seguimento. Na visita final, apenas 3 olhos apresentavam fluído subretiniano, 3 demonstravam fibrose e 15 (65,2%) apresentavam atrofia. A espessura macular central reduziu de 340,7±114,9 µm para 228,7±38,6 no final do seguimento (p<0,05). A coróide dos olhos tratados era mais espessa, mas a coriocapilar apresentava menor fluxo vascular em comparação com olhos não tratados. Apenas uma sessão de TFDs foi necessária em 19 olhos e 4 realizaram duas sessões.

CONCLUSÃO: A TFD *standard* guiada por ICGA é um procedimento seguro, sem efeitos adversos graves oculares ou sistémicos. Após 13 anos, apenas 17,4% dos casos necessitaram de 2 sessões. Porém, dois terços dos casos apresentaram atrofia na última consulta, o que provavelmente está relacionado com a progressão das alterações degenerativas da doença, limitando a melhoria da acuidade visual a longo prazo.

PALAVRAS-CHAVE: Coriorretinopatia Serosa Central/tratamento farmacológico; Fotoquimioterapia; Verteporfina/uso terapêutico.

INTRODUCTION

Central serous horioretinopathy (CSC) is a chorioretinal disease characterized by idiopathic serous neurosensory retinal detachments at the posterior pole of the fundus.[1-8] CSC commonly affects young-to-middle-aged men[6,9,10] and although the exact cause of CSC is unclear, its pathogenesis is thought to be related to abnormalities of the retinal pigment epithelium (RPE) and/or choroid,[1,10-12] Risk factors include the use of corticosteroids, psychological stress, type A personality, among others. Despite the cause, the final pathway seems to be related to choroidal vascular hyperpermeability, resulting in leakage and accumulation of subretinal fluid (SRF).[1,3- 5,7,9-11]

Indocyanine green angiography (ICGA) characteristically shows multifocal areas of choroidal abnormalities, such as vascular filling delay, congested and dilated choroidal vessels, choroidal staining, and hyperfluorescent areas in late frames of the angiogram.[1,2,4,5,8-11] Optical coherence tomography angiography (OCTA) is a noninvasive method that allows a direct insight into choriocapillaris perfusion and vasculature patterns, without the need for a dye injection.[4,5,8] Previous studies using OCTA among CSC patients have reported irregular flow patterns, involving choriocapillaris dilatation with increasing flow signals, and focal or defused dark areas with flow signal voids, corresponding to the ICGA abnormalities.[4,5] Other studies using enhanced-depth imaging (EDI) optical coherence tomography (OCT) or Swept-Source OCT (SS- OCT) have shown a thickened choroid and/or dilated choroidal vessels in patients with CSC, which might indicate increased hydrostatic pressure.[7,8,13]

CSC is subcategorized in 2 categories: acute CSC and

chronic CSC (cCSC). Acute CSC usually is self-limiting and has a good prognosis, with normal vision returning within 3 or 4 months in the majority of cases.[1,3,4,6,7,10] However, the recurrence rate is up to 50% without any treatments and 10% of patients have more than 3 recurrences when the follow-up lasts for 15 years.[6,8] In cases with persistent SRF and more extensive retinal and choroidal damage, characteristic of cCSC, significant central visual impairment or permanent symptoms and changes of the outer segments of the photoreceptors and retinal pigment epithelium (RPE) may occur.[1-4,6-9]

Treatment should be considered after 3 months without resolution of acute CSC and in chronic CSC.[1] ICGA-guided photodynamic therapy (PDT) has been shown to be an effective angiomodulator treatment of cCSC.[1-5,7,9,10,12] The primary target of treatment is the inner choroid, leading to a short-term narrowing of choroidal vessels and long-term vascular remodeling, thus reducing extravascular leakage.[1-5,7,9,10,12]

Many studies have been published since the first report produced by Yannuzzi *et al*[15] in 2003, and numerous protocols have been tested: standard-fluence PDT, half-dose PDT, half-fluency PDT, and half-time PDT.[1,9,11] Possible complications of conventional PDT are: RPE and neuroretinal atrophy, choroidal ischemia, and secondary choroidal neovascularization (CNV).[3,5,7,10,12,16]

PDT causes a far less destructive effect on the RPE compared to other treatment methods introduced in the past, such as focal laser photocoagulation.[14] It can result in visual improvement, shortened duration of symptoms and reduced recurrence rates, with a good safety profile.[16] Long-term studies, up to 4 years and 6 months, showed noteworthy improvements in visual and anatomic outcomes with low recurrence rates with full-fluence PDT for cCSC.[1,7,17] Another study conducted by Rouvas *et al*[18] demonstrated that the application of standard PDT is efficient, providing anatomic and functional improvement in the treated eyes, with a low recurrence rate of 13.4% after a mean follow-up period of 35.8 ±16.6 months. In the last-mentioned study, none of the patients presented adverse effects, reinforcing the efficacy and safety of the proposed method.

Modifications of PDT parameters have been attempted and have shown similar efficacy to standard PDT in terms of anatomical and visual outcomes, and usually with fewer complications.[5,7] Nevertheless, there are limited studies with large sample size and long-term follow-up to provide evidence regarding the long-term efficacy and safety of PDT in cCSC, especially full-fluence PDT.[1,2,7,9,17] Furthermore, studies on the long-term choroidal vascular effects of PDT by non-invasive methodologies such as SS- OCT and OCTA are few in the literature.

The aim of this report is to evaluate the 13-year follow-up of chronic CSC patients treated with standard-fluence PDT and to explore the long-term microstructural and vascular retinal and choroidal changes related to the disease and treatment. To the best of our knowledge, this is the longest follow-up ever studied for the treatment of cCSC with PDT.

MATERIAL AND METHODS

A retrospective, interventional case-series analysis with a cross-sectional evaluation was conducted on 18 patients with cCSC, treated with standard PDT, and with at least 13 years of follow-up in Coimbra's University Hospital Center. This study followed the tenets of the Declaration of Helsinki 2013, and the approval of the Institution Review Board was obtained.

The inclusion criteria were: 1) chronic CSC diagnosed with fluorescein angiography (FA) and confirmed by ICGA and OCT; 2) patient's age 18 years or older; 3) persistent CSC of >6-month duration or RPE changes induced by multifocal recurrent detachment associated with symptoms of cCSC lasting at least 6 months; 4) the provision of written informed consent. The following were exclusion criteria: 1) the presence of any other macular conditions that might compromise visual acuity; and 2) hepatic insufficiency, known hypersensitivity to fluorescein, or any other condition that might contraindicate PDT or angiographic examinations.

The presence of diffuse or poorly defined widespread areas of leakage in FA, originating from broad areas of RPE damage, made the diagnosis of cCSC. ICGA was performed to verify the presence of choroidal vascular hyperpermeability, to calculate its size, and to guide the PDT if indicated. Baseline evaluation involved best-corrected visual acuity (BCVA) with Early Treatment Diabetic Retinopathy Study chart, fundus eye examination, FA (Topcon TRC-50 IA; Topcon, Tokyo, Japan), ICG-A (Topcon TRC 50-IA; Topcon), and OCT (OCT Stratus 3; Carl Zeiss Meditec, Dublin, CA). The OCT was intended for monitoring and measuring the SRF, for evaluating structural changes of the neurosensory retina and RPE and the presence of intraretinal cysts, and to measure the central macular thickness (CMT). CMT was defined as the average thickness of the central 1 mm diameter of the ETDRS grid. During all follow-up, NRT and SRF height were manually measured in Stratus 3 OCT. To calculate NRT, markers were positioned on the fovea centralis, between the internal limiting membrane and the anterior limit of the subretinal fluid. To determine the SRF thickness, markers were placed between the anterior limit of the SRF and the RPE, without including it. The sum of the neural retina thickness and the subretinal fluid thickness corresponds to total CMT. *Baseline* retinal atrophy was reevaluated in OCT and redefined as complete RPE and outer retinal atrophy (cRORA).[19]

All patients were treated with standard PDT with verteporfin, according to the recommended protocol for CNV secondary to age-related macular degeneration (Treatment of Age-Related Macular Degeneration (TAP) Study Group 1999). Every patient was administered with 6 mg/m2 of intravenous verteporfin over 10 minutes, which was then activated by a laser wavelength of 698 nm, 15 minutes after the infusion started. It used an energy intensity of 600 mW/cm2 for 83 seconds, similar to a total dose of energy of 50 J/cm2. Standard PDT was applied only to areas of choroidal hyperpermeability (plus 1 mm diameter) identified in ICGA, including the subfoveal area. Individual spots were

performed sequentially in multiple leaks separated by >2 mm because they were >1 mm diameter. Bilateral treatments were performed in the same session. Retreatment was performed when patients presented clinical evidence of persistence or recurrence. Recurrence was based on OCT findings, such as subretinal or intraretinal fluid, and was then confirmed with FA and ICGA.

Evaluations were performed every 3 months in the first year, every 6 months during the second year, and annually thereafter.

BCVA was considered improved when there was a gain of five or more letters, and vision loss when there was a decrease of at least five letters in relation to the initial visit BCVA. At each visit, besides the evaluation of BCVA and the measurement of SRF thickness and NRT, the assessment also included the number of treatments, the presence of side effects, the presence of recurrences.

All 18 patients were convoked for a last visit, in which Spectralis SD-OCT and SS-OCT (Topcon DRI OCT-1 Atlantis) were performed to measure the SRF, for evaluating structural changes of the neurosensory retina, RPE and choroid, such as development of RPE atrophy (cRORA) and/or fibrosis, and to measure the central macular thickness (CMT) and the choroidal thickness. SS-OCT and OCTA were performed in treated and non-treated contralateral eyes, in order to compare choriocapillaris' flow densities, superficial capillary plexus (SCP) and deep capillary plexus (DCP) vessel densities, and confirm the presence of signs of conversion to neovascular disease in study eyes. Fundus autofluorescence (FAF) was performed for identification of hyperfluorescent or hypofluorescent areas, descending tracts and the status of the fovea.

Statistical analyses were performed using STATA software (version 16.0). Descriptive statistics, confirmation of normality with the Kolmogorov-Smirnov test, inferential statistics using paired t-tests and uni and multivariate linear regressions were performed. For all statistical tests, a p value < 0.05 was considered statistically significant.

RESULTS

Twenty-three eyes of 18 patients were included in the study, 15 men (83.3%) and 3 women (16.7%). The patients had a mean age of 63.9 ± 8.5 years, with a minimum of 48 and a maximum of 81 years. Mean duration of cCSC, defined as the interval between *baseline* visit and treatment, was 8.5 months. All patients were followed for a mean period of 15.8 ± 1.4 years (range, 13-18 years). The mean PDT spot size was 3.390 μm. Five of the patients had bilateral CSC. Nineteen eyes (82.6%) were submitted to only one session of PDT, and the other 4 (17.4%) underwent 2 sessions. The mean number of treatments was 1.2 ± 0.4, and the foveal spot was subfoveal in 36.8%, juxtafoveal in 36.8%, extrafoveal in 21.1% and peripapillary in 5.3%. Of the 4 eyes which underwent a second session of PDT, 2 were retreated after 6 months because of the presence of subretinal fluid and cystic changes in OCT, 1 after 21 months because of recurrence of subretinal fluid, and 1 after 6 years. No systemic or ocular side effects were found to be related to the treatment.

BCVA EVOLUTION

The Initial mean BCVA was 62.7 ± 22.7 letters (range, 10-85 letters), it was 67.1 ± 22.4 letters (range, 10-90 letters) after the first year of follow-up and, in the last visit, it was 64.6 ± 19.2 letters (range, 30-85 letters). There was a statistically significant improvement ($P < 0.05$) in BCVA at the first year of follow-up, with a mean gain of 5.08 ± 10.36 letters. This gain was, however, lost at the end of follow-up, despite a final mean gain of 1.87 ± 11.9 letters ($p>0.05$). The progression of BCVA over the years is represented in Fig. 1.

Visual acuity at the end of our follow-up improved in 8 eyes (34.8%), remained unchanged in 9 eyes (39.1%), and decreased in 6 eyes (26.1%). Differences in visual acuity were not correlated with the spot nor with the number of PDT sessions.

CMT EVOLUTION

Mean CMT decreased from 340.7 ± 114.9 μm at baseline to 290 ± 152.8 μm after the first year of follow-up. It was 228.7 ± 38.6 μm at the end of the follow-up. There was both a statistically significant decrease ($p < 0.05$) in this measure, when comparing baseline to one-year follow-up, and to the final (Fig. 2).

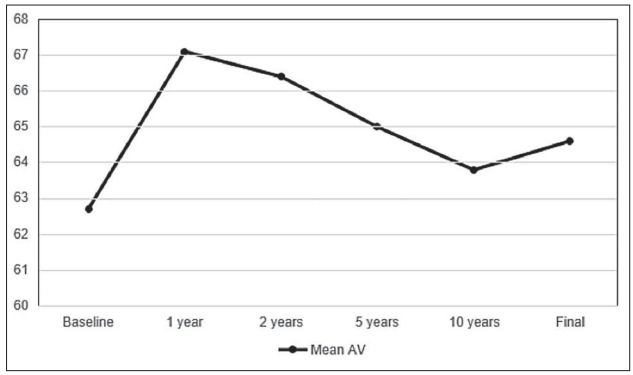


Figure 1. Progression of BCVA over the years (15.8 1.4 years), using ETDRS Scoring Method.

MORPHOLOGIC RESULTS

The morphologic results were evaluated by OCT. Subretinal fluid was found in all eyes, RPE proliferation in 9.1% and atrophy in 9.1% of the eyes at *baseline*. At the end of our follow-up, only 3 eyes (13.04%) presented subretinal fluid, 3 (13.04%) had fibrosis and 15 (65.2%) showed some degree of atrophy at the final visit. The 3 eyes who presented SRF in the last OCT had a final BCVA of 85, 45 and 35 letters. The first 2 underwent only one session of PDT, and the latter 2 sessions. Mean BCVA of the eyes which presented at-

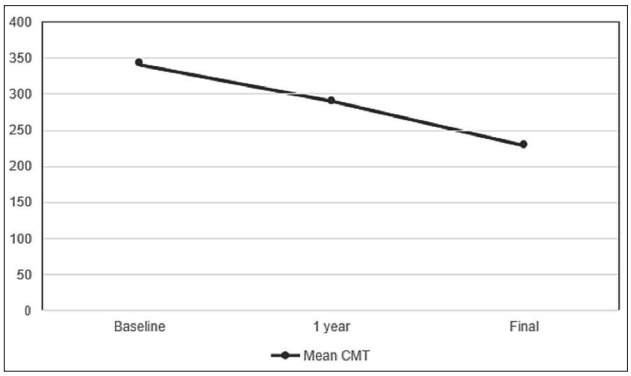


Figure 2. Progression of CMT over the years (15.8 ± 1.4 years), evaluated by OCT.

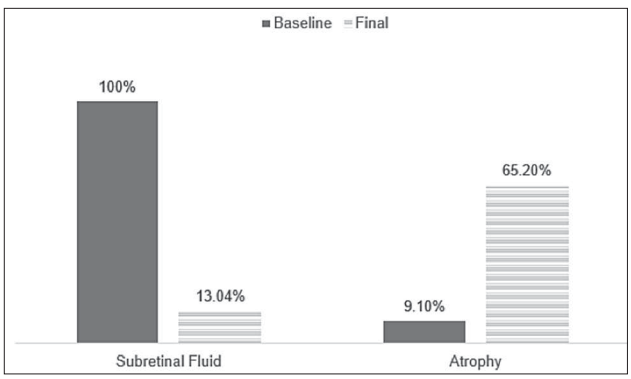


Figure 3. Comparison of retinal norphologic changes, assessed by OCT, between baseline and the end of the follow-up.

rophy in the last visit was 60.7 ± 21.3 letters, and in the eyes without atrophy in the last visit, it was 71.9 ± 12.5. However, this difference was not statistically significant. When comparing the presence of atrophy in the last visit OCT with the number of treatments, the foveal spot and *baseline* CMT, we found there was no statistically significant relation between these variables ($P > 0.05$). However, out of the eyes in which PDT spot involved the fovea (36.8%), 57.1% presented atrophy in the OCT at the final visit, while only 14.3% showed atrophy at baseline. This difference was not statistically significant.

In the final visit, the FAF showed that 12 eyes (57.1%) had hyperfluorescent areas, which represent cellular suffering, 17 eyes (80.9%) showed hypofluorescent areas, which represent cellular death, 4 eyes (19.1%) presented descending tracts, and 17 eyes (80.9%) exhibited alterations affecting the fovea (both hyper and hypo-autofluorescent changes).

CHOROIDAL'S STRUCTURAL LONG-TERM CHANGES

The final mean subfoveal choroidal thickness of treated eyes was 262.4 ± 87.86 μm. As for the untreated contralateral eyes, this value was 234.3 ± 24.5 μm. No significant differences between treated and non-treated eyes were found ($p > 0.05$), despite CSC treated eyes having in average a thicker choroid.

The OCTA was used to compare the choriocapillaris' flow density and SCP and DCP vessel densities, in both treated and non-treated contralateral eyes. We found there was no statistically significant difference ($p > 0.05$) between each of these measurements, when comparing treated eyes with non-treated contralateral eyes (Table 1). BCVA at the end of our follow-up was not associated with the choriocapillaris' flow density, nor with SCP and DCP vessel densities of treated eyes ($p > 0.05$). There were also no cases of CNV, nor other signs related to progression to neovascular disease found in OCTA in the final visit.

Table 1. Comparison between treated and non-treated eyes with PDT regarding capillary plexus density and the flow density of the choriocapillaris.

	Choriocapillaris' flow density	SCP vessel density	DCP vessel density
Treated	199.9 ± 630.1	48.5 ± 4.8	45.9 ± 3.8
Non-treated	239.7 ± 731.6	47.7 ± 4.6	46.8 ± 5.1

DISCUSSION

In the current report, we analyze the long-term results of treatment with standard PDT with verteporfin in cCSC, and we also explore the associated structural and vascular choroidal changes. We found that visual acuity outcome was not associated with the foveal spot location nor with the number of PDT sessions, although the pattern of visual improvement can be influenced by the progression of atrophic changes associated with the disease. Only 17.4% of cases needed two sessions, and there was no case of progression to choroidal neovascularization. However, about two-thirds of the cases presented atrophy in the last visit.

CSC is not a completely benign disease, as RPE atrophy and the associated visual loss seen in chronic and persistent CSC is a slow but continuous process.[20-22] Different treatments have been previously proposed in managing cases of chronic or persistent CSC, and even though some might offer a more rapid resolution of SRF as, for example, focal laser at the RPE layer, these treatments did not affect the final functional outcomes and the recurrence rate of the disease.[20] PDT is generally recommended for cCSC, and recent theories lead us to believe its mechanism of action is related to the release of free radicals that damage endothelium, reducing choroidal vasculature hyperpermeability and extravascular leakage, and provoking long-term vascular remodeling.[12,23-25] However, there is a lack of studies on the

long-term effects of PDT in cCSC. Our report is the first to describe the efficacy, safety and the chorioretinal changes 13 or more years after standard PDT for cCSC.

If left untreated, cCSC can lead to irreversible changes in the neurosensory retina, progressive damage of RPE, and consequential worse visual prognosis.[1,26] Currently, there are no standard therapeutic protocols for cCSC. Although, many other studies have shown that ICGA-guided verteporfin PDT with a standard protocol could be effective in chronic CSC, with both visual and anatomical improvement reducing the SRF. Photodynamic therapy enables constriction of inner choriocapillaris vessels followed by long-term vascular remodeling and also choriocapillaris hypoperfusion.[20,27,28]

Vasconcelos *et al*[12] reported that 5 years after standard PDT, all 17 eyes of the 15 patients included in their study had complete resolution of SRF, with a significant improvement in mean BCVA and reduction in choroidal thickness. In our report, visual acuity improved in 34.8%, and decreased in 26.1%. After one year of treatment, gain in visual acuity was significant, however this was lost at the end of follow-up, with a final mean gain of only 1.87 ± 11.9 letters. The average number of treatments was 1.2 ± 0.4.

Furthermore, 82.6% of eyes were submitted to one session of PDT, while 17.4% (4 eyes) underwent 2 sessions, either because of persistence of SRF, or because of presence of SRF and cystic changes in OCT. Differences in visual acuity outcome were not associated with the foveal spot location nor with the number of PDT sessions each eye underwent. Three eyes presented SRF in the last OCT. The first 2 underwent only one session of PDT, and the latter 2 sessions. Another study by Silva *et al*[1] found that 93.4% eyes had SRF resolution and the mean BCVA improved significantly from 58.8 letters to 66.9 letters at the end of a 4-year follow-up period. The anatomical success rate in our study was comparable to these studies. However, our pattern of visual improvement was different from observed in latter studies. This could be due to longer follow-up with progression of atrophic changes. Retinal pigment epithelium atrophy, chorioretinal scars, and choroidal hypoperfusion, all of which can cause outer retinal layer attenuation, have been assigned to standard PDT.[1] At the end of our ≥ 13-years follow-up, resolution of subretinal fluid occurred in 87% of cases, 13% had fibrosis and 65% showed atrophy at the final visit. Furthermore, out of the eyes which PDT spot involved the fovea (46.8%), 57.1% presented atrophy in the OCT at the final visit, while only 14.3% were showing atrophy at *baseline*. However, the number of treatments, the foveal spot location and *baseline* CMT had no statistically significant relation to atrophy in the last visit. Therefore, despite being difficult to draw definite conclusions regarding the impact of PDT in atrophy development, and therefore in final BCVA, this long-term finding could be due only to the chronicity of the disease and its preferential location in the central macula, and not to treatment itself.

No systemic or ocular side effects were found to be related to the treatment. Piccolino *et al*[29] noted a 12.5% retreatment rate in 9 months of follow-up. A study by Tarantola et al30, with an average follow-up of 21.9 months, established that 27.3% (3 of 11 years) required 2 treatment sessions because of reappearance of subretinal fluid. Our rate of treatment is similar to other series with shorter follow-up.

OCTA was performed in both untreated and PDT-treated eyes to assess the density of the capillary plexus vasculature and the flow density of the choriocapillaris layer. No significant differences between treated and non-treated eyes were found, despite CSC treated eyes having in average a thicker choroid. Other studies using OCT or SS-OCT have shown a thickened choroid and/or dilated choroidal vessels in patients with CSC, which might indicate increased hydrostatic pressure in the choroid.[7,8,13] These leads us to conclude these changes are associated with the disease itself, rather than with PDT. Interestingly, untreated eyes showed a higher mean vascular density of the choriocapillaris compared to treated eyes (239.7 μm *vs*. 199.9 μm). This might be explained by the remodelling of the choriocapillaris vasculature resulting from the treatment or the natural progression of the disease, in which compression by dilated choroidal vessels causes progressive atrophy of the choriocapillaris, or from both.

No cases of CNV nor other signs related to progression to neovascular disease were found in treated eyes. Therefore, neovascularization does not appear to be related to PDT, nor does any ischemia induced in the choroid seem to be caused by this treatment. In the same study previously mentioned, Vasconcelos *et al*[12] observed that morphological and functional chorioretinal changes were not correlated with the location of the treatment, neither with the progression of visual acuity, and are more likely to be related to the disease itself than with the treatment provided. In our report, no systemic adverse effects were noticed as well, which confirms previous results showing PDT with verteporfin as a safe method in the treatment of cCSC. However, there were some recurrences, and cases of RPE atrophy were observed in the OCT at the final visit, limiting visual gains in the long-term.

Our study has several limitations, including the retrospective design, the use of Stratus 3 OCT, not being able to follow-up the outer retinal layers alterations since baseline, the small sample size, and the fact that we did not compare the outcomes of full-fluence PDT and half-fluence PDT, which is now more commonly used in clinical practice. Additionally, the irregularity of the follow-up (every 3 months in the first year, every 6 months during the second year, and annually thereafter), especially due to cases of patients who would miss visits, may also be considered a limitation in this study, even so unscheduled visits were allowed in the presence of symptoms. Nevertheless, to the best of our knowledge, this is the longest follow-up (an average of 16 years) of treatment outcomes of full-fluence PDT in cCSC to date.

In conclusion, our results support the long-term effectiveness and safety of standard PDT with verteporfin, as a treatment for cCSC. These results are extremely relevant in the comprehension of the role of PDT in chronic CSC, considering this is a disease without any standard therapeutic

protocols established. Furthermore, randomized, prospective multicentre studies with large samples on the long-term effects of PDT are necessary to determine the guidelines of this treatment, in order to prevent recurrences and ocular or systemic adverse effects.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

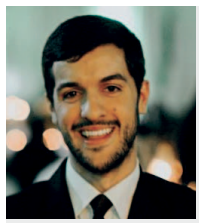
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

Provenance and Peer Review: Not commissioned; externally peer reviewed.

REFERENCES

1. Silva RM, Ruiz-Moreno JM, Gomez-Ulla F, Montero JA, Gregório T, Cachulo ML, et al. Photodynamic therapy for chronic central serous chorioretinopathy: a 4-year follow- up study. Retina. 2013;33:309-15. doi: 10.1097/IAE.0b013e3182670fbe. PubMed PMID: 23095766.
2. Rouvas A, Stavrakas P, Theodossiadis PG, Stamatiou P, Milia M, Giannakaki E, et al. Long-term results of half-fluence photodynamic therapy for chronic central serous chorioretinopathy. Eur J Ophthalmol. 2012;22:417-22. doi: 10.5301/ejo.5000051.
3. Karakus SH, Basarir B, Pinarci EY, Kirandi EU, Demirok A. Long-term results of half-dose photodynamic therapy for chronic central serous chorioretinopathy with contrast sensitivity changes. Eye. 2013;27:612-20. doi: 10.1038/eye.2013.24.
4. Xu Y, Su Y, Li L, Qi H, Zheng H, Chen C. Effect of Photodynamic Therapy on Optical Coherence Tomography Angiography in Eyes with Chronic Central Serous Chorioretinopathy. Ophthalmologica. 2017;237:167-72. doi: 10.1159/000456676.
5. Liu J, Chen C, Li L, Xu Y, Yi Z, He L, et al. Assessment of choriocapillary blood flow changes in response to half-dose photodynamic therapy in chronic central serous chorioretinopathy using optical coherence tomography angiography. BMC Ophthalmol. 2020;20:402. doi: 10.1186/s12886-020-01674-9.
6. Liu B, Deng T, Zhang J. Risk factors for central serous chorioretinopathy: A Systematic Review and Meta-Analysis. Retina. 2016;36:9-19. doi: 10.1097/iae.0000000000000837.
7. Son BK, Kim K, Kim ES, Yu SY. Long-Term Outcomes of Full-Fluence and Half- Fluence Photodynamic Therapy for Chronic Central Serous Chorioretinopathy. Ophthalmologica. 2019;241:105-15. doi: 10.1159/000490773.
8. Alovisi C, Piccolino FC, Nassisi M, Eandi CM. Choroidal Structure after Half-Dose Photodynamic Therapy in Chronic Central Serous Chorioretinopathy. J Clin Med. 2020;9:9. doi: 10.3390/jcm9092734.
9. van Rijssen TJ, van Dijk EHC, Dijkman G, Boon CJF. Clinical characteristics of chronic central serous chorioretinopathy patients with insufficient response to reduced- settings photodynamic therapy. Graefes Arch Clin Exp Ophthalmol. 2018;256:1395- 402.. doi: 10.1007/s00417-018-4003-z.
10. Haga F, Maruko R, Sato C, Kataoka K, Ito Y, Terasaki H. Long-term prognostic factors of chronic central serous chorioretinopathy after half-dose photodynamic therapy: A 3-year follow-up study. PLoS One. 2017;12:e0181479. doi: 10.1371/journal.pone.0181479.
11. Erikitola OC, Crosby-Nwaobi R, Lotery AJ, Sivaprasad S. Photodynamic therapy for central serous chorioretinopathy. Eye. 2014;28:944-57. doi: 10.1038/eye.2014.134.
12. Vasconcelos H, Marques I, Santos AR, Melo P, Pires I, Figueira J, et al. Long- term chorioretinal changes after photodynamic therapy for chronic central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol. 2013;251:1697-705. doi: 10.1007/s00417-013-2270-2..
13. Ma DJ, Park UC, Kim ET, Yu HG. Choroidal vascularity changes in idiopathic central serous chorioretinopathy after half-fluence photodynamic therapy. PLoS One. 2018;13:e0202930. doi: 10.1371/journal.pone.0202930.
14. Hwang S, Noh H, Kang SW, Kang MC, Lee D, Kim SJ. Choroidal neovascularization secondary to photodynamic therapy for central serous chorioretinopathy: Incidence, Risk Factors, and Clinical Outcomes. Retina. 2021;41:1762-70. doi: 10.1097/iae.0000000000003067.
15. Yannuzzi LA, Slakter JS, Gross NE, Spaide RF, Costa D, Huang SJ, et al. Indocyanine green angiography-guided photodynamic therapy for treatment of chronic central serous chorioretinopathy: a pilot study. Retina. 2003;23:288-98. doi: 10.1097/00006982-200306000-00002.
16. Lai FH, Ng DS, Bakthavatsalam M, Chan VC, Young AL, Luk FO, et al. A Multicenter Study on the Long-term Outcomes of Half-dose Photodynamic Therapy in Chronic Central Serous Chorioretinopathy. Am J Ophthalmol. 2016;170:91-9. doi: 10.1016/j.ajo.2016.07.026.
17. Tseng CC, Chen SN. Long-term efficacy of half-dose photodynamic therapy on chronic central serous chorioretinopathy. Br J Ophthalmol. 2015;99:1070-7. doi: 10.1136/bjophthalmol-2014-305353.
18. Rouvas A, Nikita E, Chatziralli I, Ladas I, Androu A, Theodossiadis P. Long-term follow-up of standard photodynamic

therapy with standardized small spot size for diffuse retinal pigment epitheliopathy. Eur J Ophthalmol. 2015;25:229-34. doi: 10.5301/ejo.5000541.
19. Sadda SR, Guymer R, Holz FG, Schmitz-Valckenberg S, Curcio CA, Bird AC, et al. Consensus Definition for Atrophy Associated with Age-Related Macular Degeneration on OCT: Classification of Atrophy Report 3. Ophthalmology. 2018;125:537-48. doi: 10.1016/j.ophtha.2017.09.028.
20. Chan WM, Lam DS, Lai TY, Tam BS, Liu DT, Chan CK. Choroidal vascular remodelling in central serous chorioretinopathy after indocyanine green guided photodynamic therapy with verteporfin: a novel treatment at the primary disease level. Br J Ophthalmol. 2003;87:1453-8. doi: 10.1136/bjo.87.12.1453.
21. Robertson DM. Argon laser photocoagulation treatment in central serous chorioretinopathy. Ophthalmology. 1986;93:972-4. doi: 10.1016/s0161- 6420(86)33652-2.
22. von Winning CH, Oosterhuis JA, Renger-van Dijk AH, Hornstra-Limburg H, Polak BC. Diffuse retinal pigment epitheliopathy. Ophthalmologica. 1982;185:7-14. doi: 10.1159/000309216.
23. Sartini F, Figus M, Nardi M, Casini G, Posarelli C. Non-resolving, recurrent and chronic central serous chorioretinopathy: available treatment options. Eye. 2019;33:1035-43. doi: 10.1038/s41433-019-0381-7.
24. Park W, Kim M, Kim RY, Park YH. Comparing effects of photodynamic therapy in central serous chorioretinopathy: full-dose versus half-dose versus half-dose-half- fluence. Graefes Arch Clin Exp Ophthalmol. 2019;257:2155-61. doi: 10.1007/s00417-019-04426-8.
25. Altinel MG, Kanra AY, Totuk OMG, Ardagil A, Kabadayi K. Comparison of half- dose versus half-fluence versus standard photodynamic therapy in chronic central serous chorioretinopathy. Photodiagnosis Photodyn Ther. 2021;33:102081. doi: 10.1016/j.pdpdt.2020.102081.
26. Jalkh AE, Jabbour N, Avila MP, Trempe CL, Schepens CL. Retinal pigment epithelium decompensation. I. Clinical features and natural course. Ophthalmology. 1984;91:1544-8. doi: 10.1016/s0161-6420(84)34095-7.
27. Schmidt-Erfurth U, Hasan T, Gragoudas E, Michaud N, Flotte TJ, Birngruber R. Vascular targeting in photodynamic occlusion of subretinal vessels. Ophthalmology. 1994;101:1953-61. doi: 10.1016/s0161-6420(13)31079-3.
28. Schmidt-Erfurth U, Hasan T. Mechanisms of action of photodynamic therapy with verteporfin for the treatment of age-related macular degeneration. Surv Ophthalmol. 2000;45:195-214. doi: 10.1016/s0039-6257(00)00158-2.
29. Cardillo Piccolino F, Eandi CM, Ventre L, Rigault de la Longrais RC, Grignolo FM. Photodynamic therapy for chronic central serous chorioretinopathy. Retina. 2003;23:752-63. doi: 10.1097/00006982-200312000-00002.
30. Tarantola RM, Law JC, Recchia FM, Sternberg P, Jr., Agarwal A. Photodynamic therapy as treatment of chronic idiopathic central serous chorioretinopathy. Lasers Surg Med. 2008;40:671-5. doi: 10.1002/lsm.20720.



Corresponding Author/
Autor Correspondente:

Pedro Nuno Pereira
Ophthalmology Department, Centro Hospitalar e Universitário de Coimbra (CHUC)
Praceta Prof. Mota Pinto,
3049 Coimbra, Portugal
pedro.n.pereira94@gmail.com

ORCID: 0000-0001-7835-4755