Low-fluence photodynamic therapy in chronic central serous chorioretinopathy**,

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**Objective**: To evaluate safety and efficacy of low-fluence photodynamic therapy (LFPDT) with verteporfin in patients affected with chronic central serous chorioretinopathy (CCSC), in terms of visual acuity (VA) and macular morphology measured with optical coherence tomography (OCT).

**Methods**: A retrospective, non-randomized and interventionist analysis was performed on 16 eyes in 15 patients with CCSC treated with LFPDT. Best corrected visual acuity (BCVA) with ETDRS optotypes and central foveal thickness (CFT) in OCT were evaluated as outcome measures.

**Results**: The mean follow-up was 10.8 months. The mean BCVA improved from 58.12 to 68.68 ETDRS letters, and CFT decreased from 280.5 to 172.18 μm, with subretinal fluid resolution in 14 eyes (87.5%), two of them after a second LFTPD. No complications related to treatment were recorded.

**Conclusions**: LFPDT with verteporfin can be useful in CCSC to stabilize or improve BCVA, reabsorb subretinal fluid and reduce CFT. Randomized studies with a longer follow-up are required to assure the role of this treatment and to optimize parameters for higher efficacy and safety in CCSC patients.

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Tratamiento de coriorretinopatía serosa central crónica mediante terapia fotodinámica de baja fluencia

**Resumen**

Objetivo: Evaluar la seguridad y la eficacia en términos de agudeza visual (AV) y morfología macular mediante tomografía de coherencia óptica (OCT) de la aplicación de terapia fotodinámica de baja fluencia (LFPDT) con verteporfin en pacientes afectos de coriorretinopatía serosa central crónica (CCSC).

**Método**: Análisis retrospectivo e intervencionista de casos consecutivos, no randomizados. Se siguieron un total de 16 ojos de 15 pacientes afectos de CCSC tratados con LFPDT.
Se evaluaron mejor agudeza visual corregida (MAVC) mediante escala de optotipos ETDRS y grosor foveal central (CFT) en OCT como indicadores de resultados.

Resultados: El seguimiento medio fue de 10,8 meses. La MAVC media mejoró de 58,125 a 68,68 letras ETDRS, y el CFT se redujo de 280,5 a 172,16 micras, con desaparición del fluido subretiniano en 14 de los casos (87,5%), en 2 de ellos tras una segunda aplicación de LFPDT. No se registraron complicaciones asociadas al tratamiento.

Conclusiones: LFPDT con verteporfina puede ser útil en CCSC para estabilizar o mejorar MAVC y reabsorber el fluido subretiniano y reducir el CFT. Se requieren estudios razonados con seguimiento más prolongado para confirmar el papel de este tratamiento y optimizar los parámetros que permitan mayor eficacia y seguridad en su aplicación en pacientes afectos de CCSC.

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Introduction

Idiopathic central serous chorioretinopathy (CSC) consists in an alteration characterized by the accumulation of transparent fluid in the posterior pole of the fundus. There is a chronic variant which is also known as retina diffuse pigment epitheliopathy in which a diffuse alteration of the RPE pigmentation is identified in association with the chronic presence of subretinal fluid (SRF). Even though CSC is generally a self-limited disease with good visual prognosis, the cases exhibiting chronic characteristics usually associate a significant long-term visual compromise.

The origin of the disease remains unclear, although the findings made with fluorescein angiography (FA) and indocyanine green showing the presence of leak points at the level of the retina pigment epithelium (RPE) associated to choroidal vascular hyper permeability have been demonstrated. Increased choroidal hydrostatic pressure is deemed to be the cause of the alteration of the RPE barriers and the exit of fluid into the subretinal space.

Various treatment modes have been suggested to diminish the visual involvement in these patients. The efficacy of argon laser photocoagulation on the leak points is controversial because, although it has proven to accelerate the reabsorption of SRF but has not evidenced long-term vision improvements or diminished the amount of relapses, without forgetting the well-known complications associated to its application such as the inadvertent coagulation of the fovea, the induction of choroidal neovascularization (CNV) or the progressive enlargement of the RPE atrophy area caused by the laser.

In recent years, and with the premise of reducing the vascular flow in a hyper-permeable choriocapillary layer, numerous papers have described benefits of photodynamic therapy treatment (PDT) with verteporfin to achieve anatomical and functional recovery in CCSC cases. The application of PDT at standard doses for CNV (according to the criteria of the 1999 TAP study group) has achieved promising results but is not free of complications, notably the appearance of CNV, severe choroidal ischemia and RPE atrophy. In order to minimize the risk of said complications, the following steps endeavored to modify the usual PDT parameters. Accordingly, it has been suggested to reduce the verteporfin dose, and this paper presents the application of LFPDT, which consists in a modification of the standard parameters, applying a fluence of 25J/cm² and an intensity of 300 mW/cm². This involves a 50% reduction of the laser beam applied to the retina in order to minimize undesirable effects on a healthy retina.

Subjects, material and methods

A retrospective and interventionist analysis of non-randomized consecutive cases was performed comprising 16 eyes of 15 patients diagnosed with chronic central serous chorioretinopathy between 2007 and 2009 in the Bellvitge University Hospital.

Inclusion criteria:

(1) diagnosis by means of ophthalmological assessments confirmed with FA and OCT,
(2) clinic comprising at least 5 months,
(3) age over 18,
(4) absence of a spontaneous improvement or induced by means of empirical treatment,
(5) signature of informed consent.

Exclusion criteria:

(1) previous laser photocoagulation treatment,
(2) liver insufficiency, known allergy to fluorescein or other conditions making PDT contraindicated.

Prior to the treatment a full ophthalmological assessment was made, including best corrected visual acuity (BCVA) utilizing ETDRS optotypes at 4 m, FA and OCT. The follow-up was made assessing BCVA and OCT (Figs. 1 and 2). As the study was retrospective, the results of the first control made between month 3 and 6 after the application of PDT and a second control between month 9 and 12 post-treatment were grouped. The patients were treated with LFPDT with verteporfin applying the laser centered on the fovea because all the cases exhibited subfoveal SRF with multiple leak points, varying the size of the spots in order to act thereupon in a single session, always respecting one disc diameter of distance from the optic nerve (Fig. 3). The usual protocol was followed, modifying the fluence and intensity parameters 50% as described in Table 1.
Fig. 1 – Case 1: female, 51, CSCC with 15-month evolution. Initial VA of 70 letters. Retinography and OCT prior to treatment, showing SRF below the macula (blue arrows) and subfoveal yellowish pigmented deposits (black arrow).

Fig. 2 – Case 1: retinography and OCT 12 months post-treatment, showing complete reabsorption of SRF with persistence of subfoveal deposits. Final VA of 85 letters.

Fig. 3 – Case 2: male, 41, CCSC with five-year evolution and VA of 62 letters. (A) Initial FA: multiple leak points. (B) OCT pre-treatment: central retina neurosensory detachment. (C) OCT at month 12: neurosensory detachment resolved. Final VA of 70 letters.
Table 1 – Parameters utilized for the application of low fluence PDT. QUAD: quadspheric lens.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verteporfin dose</td>
<td>6 mg/m²</td>
</tr>
<tr>
<td>Infusion time</td>
<td>10 min</td>
</tr>
<tr>
<td>Application of laser</td>
<td>15 min after beginning the infusion</td>
</tr>
<tr>
<td>Lens</td>
<td>QUAD</td>
</tr>
<tr>
<td>Fluency</td>
<td>25 J/cm²</td>
</tr>
<tr>
<td>Intensity</td>
<td>300 mW/cm²</td>
</tr>
<tr>
<td>Application time</td>
<td>83 seg</td>
</tr>
<tr>
<td>Mean spot</td>
<td>4.285 μm (3.500–6.000 μm)</td>
</tr>
<tr>
<td>Application area</td>
<td>Macular centered on the fovea, respecting the distance of 1 DD to ON</td>
</tr>
</tbody>
</table>

The analyzed results comprised BCVA, CFT, number of LFPDT sessions and complications. BCVA and CFT changes were assessed before and after LFPDT by means of the t for Student test for paired data.

Results

The results comprised the data of 16 eyes of 15 patients, of which 11 were males and 4 females. The mean age at diagnostic time was of 51.06 years (range 38–66 years, SD 7.88). The mean duration of the disease was of 26.8 months (range 5–72 months, SD 21.09). The mean follow-up time was of 10.8 months (range 6–12 months, SD 2.48). Eleven cases exhibited unilateral involvement and 4 were bilateral, all of them males. Of the 4 cases exhibiting bilateral clinic, in 2 a wait-and-see approach was indicated in the eye with the best visual acuity, and in a further case only one eye was included, as the other one had been previously treated with the standard dose of PDT. In 4 cases SRF persistence was identified after the first treatment and a second LFPDT application was performed with complete improvement in 2 of said cases.

The mean BCVA prior to treatment was of 58.12 letters ETDRS (range 18–75 letters, SD 19.86), going to 63.64 letters in the first control (3–6 months) and to 68.68 (range 18–85, SD 18.83) in the second control (9–12 months), exhibiting statistically significant differences (p < 0.01; t for Student test) compared against baseline. The mean CFT was of 280.5 μm (SD 92.70) prior to treatment, 203.91 at the first control and 172.18 (SD 36.82) at the end of the follow-up (p < 0.01; t for Student test) (Fig. 4).

The mean variation of BCVA was of +2 ETDRS lines, reaching +3 or more lines in 3 eyes (18.75%), and +1/+2 lines in 7 eyes (43.75%), with 6 eyes (37.5%) remaining without variations against their previous BCVA. None of the cases exhibited a reduction of VA against the baseline. No additional secondary complications in the subsequent follow-up were identified.

Discussion

Multiple papers endorsed the application of PDT for treating CSC, mainly the chronic variant thereof, although there are groups that have tested its usefulness in acute CSC, such as the work by Chan et al.,28 and Zhao et al.,29 discussing the application of PDT in acute CSC to prime reduced doses of verteporfin (3 mg/m² in the first work and looking for the lowest effective dose in the second paper). Among the studies defending the benefits of CCSC, Yannuzzi et al.,13 treated 20 eyes and presented a reapplication of the serous detachment in 12, with visual improvement in 6 and stability in the remaining 14 with a mean follow-up of 6.8 months. Berthout et al.,15 treated 31 eyes (23 in chronic phase) achieving reapplication in 90.32% of cases, relapses in 12.9% and stable BCVA in the cases that did not have relapses (mean follow-up of 8 months). Ruiz-Moreno et al.,12 carried out a multicenter study including 82 eyes, with a mean follow-up of 12 months, describing fluid reabsorption in all cases and a mean BCVA improvement (logMAR) of 0.53–0.37.

The presence of eventual complications secondary to treatment have led to the search of parameters that maintain the treatment effectiveness and minimize the dose of the photosensitizer, varying the infusion times or, as in our work, applying low fluence parameters. This principle is based on the fact that the fluence rate of the applied light is an important regulator of the tissue oxygenation and the treatment results,30 and the reduction thereof can achieve an effective microvascular damage effective for treating the desired areas without compromising the surrounding healthy tissue.31 The
verification of these facts in tumor as well as ophthalmological pathology has enabled its application in myopic neovascular pathology and in CCSC. In this regard, the work by Reibaldi et al. is worthy of note. They carried out a prospective, multicenter, masked and nonrandomized study comparing standard treatment versus low fluence in 42 patients. They presented 23 cases treated with low fluence and 19 with standard fluence. In both groups they obtained significant visual improvement (of 0.43–0.24 logMAR in the standard-fluence group and of 0.46–0.16 in the low-fluence group, both at month 12 and without significant differences between them), but with a lower incidence of adverse effects. They described one case of CNV and a higher degree of choroidal hypo-perfusion among the patients treated with standard PDT.

Both in the above-mentioned papers as well as in our work we find a bias, i.e., the absence of a control group enabling the confirmation of the assumed improvement against the natural evolution of the disease. In our case, additional limitations involved a reduced sample and shorter follow-up periods, although the input received to date allows us to state that LF-PDT with verteporfin can be a safe and efficient technique that improves or at least stabilizes BCVA, reabsorbs SRF and reduces CFT, without any observed complications. Comparative studies would be required to confirm the hypothesis that it is possible to diminish the rate of complications vis-à-vis the application of standard PDT in patients affected by CCSC.

Conflicts of interest

No conflict of interests have been reported by the authors.

References


