ORIGINAL ARTICLE

Long-term results of low-fluence photodynamic therapy for chronic central serous chorioretinopathy

Résultats à long terme de la photothérapie dynamique en fluence réduite pour les choriorétinites séreuses centrales chroniques

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KEYWORDS
Chronic central serous chorioretinopathy; Low-fluence; Photodynamic therapy; Choroidal vascular hyperpermeability; Macular neurosensory detachment; Serous retinal detachment; Verteporfin

Summary
Purpose. — To evaluate long-term results of low-fluence photodynamic therapy (PDT) with verteporfin in the treatment of chronic central serous chorioretinopathy (CCSC).
Methods. — Retrospective medical record review of 38 eyes (34 patients) who received low-fluence PDT for the treatment of CCSC. Visual acuity (VA), fundus biomicroscopy, fluorescein angiography (FA), indocyanine green angiography (ICG) and optical coherence tomography (OCT) were analyzed.
Results. — Thirty-eight eyes (34 patients) with CCSC received low-fluence PDT. Mean follow-up after PDT was 43.97 months. Mean logMar best corrected VA (BCVA) improved significantly from 0.33 to 0.11 at the last follow-up which corresponds to a gain of 2.2 lines. At 3 months, complete resolution of central subretinal fluid was achieved on OCT after 1 PDT in 37 eyes and after 2 PTDs in 1 eye (retreated at 3 months after first PDT). One patient developed choroidal neovascularization (CNV) 4 years after his low-fluence PDT and received anti-vascular endothelial growth factor (VEGF) injections.

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Introduction

Central serous chorioretinopathy (CSC) is an idiopathic disease characterized by a macular detachment of the neurosensory retina. The etiology of this disease remains unclear and many theories have emerged since the 1960s. Early studies based on fluorescein angiography showed that the macular detachment resulted from a leakage in the retinal pigment epithelium (RPE) due to a breakdown of the external blood retinal barrier. Recently, Indocyanine green angiography (ICGA) has improved the understanding of this disease by describing the choroidal circulation. ICGA shows a delay in choroidal arteries and choriocapillaris circulation causing an ischemic stress which can lead to venous congestion and choroidal hyperpermeability [1]. A disruption in the continuity of the detached RPE would then permit a leakage of the choroidal exudate [2–4]. Although the precise physiopathology of this condition remains unknown, corticosteroids either endo- or exogenous have demonstrated their importance in this condition [5,6]. The latest studies suggest that an elevation of catecholamin or an overreaction of the mineralocorticoid pathway could result in a vasodilatation and hyperpermeability of the choroidal vessels [7]. Since a few years, enhanced depth imaging optical coherence tomography (EDI-OCT) has also demonstrated its role in completing the analysis of this choroidal disease by showing an increase in choroidal thickness and lumen area of abnormal choroidal vessels [8].

CSC is also known to be associated with male gender, pregnancy, stress, Cushing’s syndrome, steroid-producing tumors and type A personality [9,10].

Acute CSC usually resolves spontaneously in 3 to 4 months and patients have a good visual prognosis [11]. However, 15 to 50% tend to develop recurrent or persistent detachment [11–13].

The long lasting detachment of the neurosensory retina combined with the decompensation of the RPE may lead to cystoid macular degeneration, foveal atrophy and damage of the photoreceptor layer with an irreversible significant vision loss of 3 lines or more in 15% to 50% of cases [14–16].

Presently, photodynamic therapy (PDT) with verteporfin and thermal laser photocoagulation (TLP) remain the best treatment options. Many studies suggest that TLP is mainly effective in acute CSC demonstrating a clear extra foveal focal leakage on FA as it offers a more rapid absorption of subretinal fluid. However, TLP can cause inadvertent coagulation of the fovea, iatrogenic RPE damage, permanent scotoma, scar formation and CNV [17,18]. On the other hand, PDT shows good anatomic and functional results in CCSC. Spaide et al. gave a well accepted definition of “chronic” CSC characterized by a serious macular elevation, visible microscopically or detected by OCT, that is associated with subtle leaks of ill-defined staining of retinal pigment epithelium on FA [4]. ICGA then shows a characteristic pattern of multifocal patchy hyperfluorescence best seen in the midphase of the ICG with dispersion of the dye.

Conclusion. — Low-fluence PDT with verteporfin for CCSC seems efficacious and safe in the long-term.

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and silhouetting of the larger choroidal vessels against a brighter background later in the angiographic sequence [19].

A PDT treatment has the advantage of reducing choroidal vascular hyperpermeability on an extended area while TLP treats the leakage point from the RPE into the subretinal space visible on fluorescein angiography [20]. Nevertheless, complications with standard fluence PDT have also been described such as foveal atrophy, RPE changes, choriocapillaris ischemia and secondary choroidal neovascularization (CNV) [21—25].

Therefore, the use of modified PDT parameters such as low-fluence PDT have been evaluated by some authors [26,27] and shows encouraging results with a significant reduction of side effects.

In addition of supporting the effectiveness of low-fluence PDT in the treatment of CCSC, and since long-term studies are few, our study aims to demonstrate the maintenance of good results over time.

Materials and methods

Retrospective review of medical records of 38 eyes of 34 consecutive patients with CCSC.

Patients included in our study showed serous macular elevation on fundus examination, confirmed by OCT in association with RPE atrophic areas and subtle leaks of ill-defined staining by FA according to Spaida’s definition. Patients received low-fluence PDT between January 2003 and September 2013 at Brugmann and Erasme Brussels University Hospitals, Belgium. Most patients were referred to our center, some with a long duration of symptoms. When this was the case, treatment was performed promptly. Diagnosis of CCSC was based on funduscopy examination, fluorescein angiography (FA), ICGA (Heidelberg Retina Angiography; Heidelberg Engineering, Heidelberg, Germany) and time-domain (TD) OCT (Stratus OCT, Carl Zeiss) or high resolution spectral-domain (SD) OCT (Spectralis, Heidelberg Engineering). Exclusion criteria were:

• choroidal neovascularization at the time of the treatment;
• treatment with focal laser or any previous treatment with standard PDT, anti-VEGF and steroid intra-ocular injections and;
• associated age-related macular disease, polypoidal choroidal vasculopathy or any other macular diseases that could confound with the CCSC.

During follow-up, all patients were asked to visit us at least once during the first 6 months. Afterwards, the visits were organized every year. Snellen best corrected visual acuity and OCT examinations were performed at every visit. FA was performed in all patients at baseline, at approximately 3 months and at the last follow-up visit. ICGA was performed whenever a recurrence was suspected.

Vertepofin (visudyne®) dose was 6 mg/m² body surface area, diluted in 30 mL infusion solution, given by a 10-minute intravenous infusion. Light was applied 15 minutes after the start of infusion. All patients received a single-spot PDT treatment. The spot size was measured using the greatest linear dimension (GLD) of the area of choroidal hyperpermeability observed on ICGA. The spot size could be extended, if necessary, to areas of leakage and edema based on FA and OCT analysis. The treatment spot size was 1000 microns larger than the GLD of the lesion on the retina to allow a 500 micron border, ensuring full coverage of the lesion. The maximum spot size was 6400 μm. In this low-fluence PDT protocol, a total light energy of 25 J/cm², a light dose rate of 300 mW/cm², and a time of photosensitization of 83 seconds were used.

Analysis of retinal thickness in this study was performed using the central retinal thickness measurement whether it was on time-domain (TD) OCT (Stratus OCT, Carl Zeiss) or high resolution spectral-domain (SD) OCT (Spectralis, Heidelberg Engineering).

For statistical analysis, SPSS software version 17.0 was used. Data were analyzed using the Wilcoxon signed-rank test. Snellen BCVA was converted to logarithm of the minimal angle of resolution (logMAR) BCVA and its corresponding line number for analysis. A P value of 0.05 was considered statistically significant and tests were 2 tailed.

Results

Thirty-eight eyes from 34 patients received half-fluence PDT for CCSC. Demographic details, clinical findings and treatment results are summarized in Table 1.

The mean age of the 34 patients at the moment of treatment was 52.2 years (range, 31—68). Thirty-one patients (92%) were men and three (8%) were women. The mean follow-up period was longer than 3 years (mean: 43.97 months, range: 12—98 months; median: 42 months). The mean duration of CSC, defined by the period between first time the patient described symptoms of CSC and treatment was 3.75 years (range: 1—16 years).

All the patients showed a choroidal hyperpermeability on ICGA. Mean PDT spot size was 4410.52 μm (range, 2200—6400 μm). The spot size was extended to maximal size of 6400 μm in 10 eyes to include areas of leakage and/or edema based on FA and OCT analysis.

First follow-up examination was carried out at 1 month to 6 weeks in 33 out of 38 eyes. At that time of visit, complete resolution of central SRF was observed on OCT in 29 eyes. Central SRF resolved completely in 3 more eyes at 3 months. One patient showed persistent central serous detachment 1 and 2 months after treatment. A second low-fluence PDT was given to the patient 2 months after the first treatment. Two months after his second PDT treatment, we observed a resolution of central SRF. First follow-up examination was conducted at 3 months in 5 of the 38 eyes with disappearance of central SRF on OCT in all of them.

Central retinal thickness (CRT) measured on time-domain (TD) OCT (Stratus OCT, Carl Zeiss) or high resolution spectral-domain (SD) OCT (Spectralis, Heidelberg Engineering) was collected before treatment and at last follow-up in 32 eyes in which measurements were conducted on the same OCT during the hole follow-up period. Mean CRT before low-fluence PDT was 348.94 μm (median: 350.5 μm, interquartile range: 266.25—395.75 μm) and at last follow-up it was 211.09 μm (median: 202.5 μm, interquartile range: 183—235.5 μm) (Fig. 1). Mean duration between those two measurements was 32.25 months (median: 24 months, range: 12—84 months). Reduction of fluid during that period.
Table 1 Patients characteristics and treatment outcomes in 34 patients (38 eyes) with chronic central serous chor-oretinopathy treated with low-fluence photodynamic therapy.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Treated eye</th>
<th>Duration of CCSC (years)</th>
<th>PDT spot (µm)</th>
<th>Baseline (LogMar)</th>
<th>BCVA last visit</th>
<th>Line gain (LogMar)</th>
<th>Follow-up (months)</th>
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M: male; F: female; OD: right eye; OS: left eye; UK: unknown; SRF: subretinal fluid; PED: pigment epithelium detachment; CME: cystoid macular edema.

was statistically significant (P < 0.0001). The measurements of the six other eyes (six patients) could not be used because of the long follow-up of those patients. Indeed, their initial central retinal thickness had been measured on TD OCT (Stratus OCT, Carl Zeiss) while later in the follow-up, retinal thickness was evaluated on SD high resolution OCT (Spectralis, Heidelberg Engineering).

Central retinal thickness measurements was available 1 to 3 months after treatment and at last follow-up in 21 eyes with a minimal follow-up of 2 years. Mean CRT in this group was 202.1 µm at the first follow-up visit (median: 182 µm; interquartile range: 168–227 µm) and at last follow-up visit it was 206.7 µm (median: 208 µm; interquartile range: 181–237 µm). The mean follow-up period was 41 months (median: 36 months; range 24–84 months). There was no significant statistical difference in mean CRT between first and last follow-up (P < 0.005).

Mean BCVA in LogMar scale at baseline was 0.33 or 0.47 in Snellen visual acuity (median 0.3, interquartile range: 0.4–0.15). At the first follow-up visit after PDT, mean logMar BCVA was 0.21 or 0.62 in Snellen visual acuity (median 0.13; interquartile range: 0.3–0.05), at six months it was 0.13 or 0.75 in Snellen visual acuity (median: 0.08 interquartile range: 0.3–0) and at last follow-up it was 0.11 or 0.78 in Snellen visual acuity (median: 0.08 interquartile range: 0.22–0). Between initial examination and last
follow-up, mean visual acuity improved by 2.2 lines in logMar scale. Throughout the follow-up period, a statistically significant improvement was observed between baseline BCVA and respectively first follow-up and 6 months mean BCVA ($P < 0.0001$). The mean BCVA (logMar) at baseline, first follow-up, 6 months and last follow-up are shown in Fig. 2.

Twenty-five eyes had a follow-up of at least 3 years (Mean period 53.28; range, 36–96 months; median, 48 months). In this group, mean BCVA (logMar) before PDT was 0.32 or 0.48 in Snellen visual acuity (median: 0.3; interquartile range: 0.4—0.15). At 1 year it was 0.09 or 0.82 in Snellen VA (median: 0; interquartile range: 0.22—0), 2 years it was 0.11 or 0.78 in Snellen VA (median: 0.025; interquartile range: 0.22—0) and at last visit it was 0.09 or 0.82 in Snellen VA (median: 0; interquartile range: 0.22—0). The improvement of visual acuity after a mean period of more than 4 years was statistically significant ($P < 0.0001$). Mean BCVA (logMar) before PDT at 1, 2 years and at last visit are shown in Fig. 3.

Visual acuity improved 3 or more lines in 16 eyes (42.11%) in logMar scale with an initial mean BCVA of 0.51 in logMar or 0.31 in Snellen VA (median: 0.4; interquartile range: 0.24—0.15) and a final mean BCVA of 0.11 in logMar or 0.82 in Snellen VA (median: 0.025; interquartile range: 0.24—0.08). In this group, mean follow-up was equal to 4 years (47.38 months; median 48 months; range 12—96). Visual improvement was statistically significant ($P < 0.0001$).

A gain of less than 1 line was observed in 2 eyes (5.26%) with an initial mean BCVA of 0.15 in logMar scale (0.7 Snellen VA) and a final BCVA of 0.17 in logMar scale (0.85 in Snellen VA) after a mean follow-up of 16 months.

Visual acuity remained stable in 5 eyes (13.16%) over a mean period of 53 months (median: 36; range: 24—108).

A loss of 0.5 lines in logMar scale was observed in 2 eyes respectively (5.26%). Their initial BCVA was 0 (1.0 in Snellen VA) for the first eye and 0.05 (0.88 Snellen VA) for the second, and their final BCVA was 0.05 (0.88 in Snellen scale) and 0.1 (0.8 in Snellen VA) respectively. Those two last patients each had a follow-up of 24 months.

The mean gain of lines between BCVA in LogMar scale before low-fluence PDT and at last follow-up visit for the total group of 38 eyes after treatment is represented in Table 2.

One patient developed juxtafoveal CNV approximately 4 years (47 months) after his low-fluence PDT treatment. His initial BCVA was 0.3 in LogMar scale (0.5 in Snellen VA) and his BCVA 3 months after low-fluence PDT was 0 in LogMar scale (1.0 in Snellen VA). His follow-up visits at respectively 1, 2 and 3 years after treatment showed no recurrence of SRF and a stabilized BCVA. When he presented 47 months after treatment, the patient described metamorphopsia without any change in VA (BCVA of 0 in LogMar scale, 1.0 in Snellen VA). Investigations showed the presence of CNV.

The patient received 5 monthly injections of ranibizumab. At his control visits 1, 2, 3, and 6 months after the last dose of Ranibizumab, there were no signs...
Table 2  Mean gain of lines between initial visit and at last follow-up visit in 42 eyes (39 patients) treated with low-fluence PDT for chronic central serous chorioretinopathy.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n (n (%)</th>
<th>Mean initial BCVA (LogMar)</th>
<th>Mean final BCVA (LogMar)</th>
<th>Mean follow-up (months)</th>
<th>P value</th>
</tr>
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<tr>
<td>Line gain ≥ 3</td>
<td>17 (38.6%)</td>
<td>0.50</td>
<td>0.1</td>
<td>40.94</td>
<td>P &lt; 0.0001</td>
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<td>Line gain ≥ 1</td>
<td>19 (43.18%)</td>
<td>0.22</td>
<td>0.08</td>
<td>36</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Line gain &lt; 1</td>
<td>2 (4.67%)</td>
<td>0.15</td>
<td>0.07</td>
<td>12</td>
<td>—</td>
</tr>
<tr>
<td>Line gain = 0</td>
<td>4 (9.10%)</td>
<td>0.18</td>
<td>0.18</td>
<td>36</td>
<td>—</td>
</tr>
<tr>
<td>Line loss</td>
<td>2 (4.67%)</td>
<td>0.38</td>
<td>0.38</td>
<td>24</td>
<td>—</td>
</tr>
</tbody>
</table>

of persisting CNV on FA, OCT and fundus examination, his symptoms had disappeared and his VA was stable. A control visit is scheduled in 1 month (1 year after ranibizumab) or earlier if the patient has any complaints. No systemic adverse events were noticed in our study.

Discussion

A precise distinction between the acute and chronic form of central serous chorioretinopathy is lacking in current literature. However, there is a general belief that the ‘acute’ form of CSC refers to a self limiting CSC that resolves spontaneously in several months without any treatment. On the other hand, Spaide et al. gave a well accepted definition of ‘chronic’ CSC characterized by a serous macular elevation associated with subtle leaks of ill-defined staining of retinal pigment epithelium on FA [4] and a multifocal patchy hyperfluorescence best seen in the midphase of the ICG indicating chorioidal hyperpermeability.

The acute form of CSC can therefore be considered as a benign condition without any treatment necessity. Unfortunately, a minority of cases progress to chronic CSC where a prolonged detachment of the macula can cause a severe and irreversible loss of vision [15,16].

Currently, there is no standard treatment for chronic CSC established by clinical trials and best treatment options remain TLP and PDT with verteporfin. Before the advent of PDT, TLP represented the only available treatment for chronic CSC. Nevertheless, if TLP can be directed at focal leaks and has been proven to accelerate the reabsorption of SRF, outcomes are variable and complications such as inadvertent coagulation of the fovea, induction of chorioidal neovascularization and progressive enlargement of the chorioretinal atrophy are well-known [17,18]. Maruko et al. studied the resolution of subretinal fluid after TLP and PDT in 12 and 8 eyes respectively. The subretinal fluid resolved in both disease groups; however, the chorioidal thickness and hyperpermeability seen during ICGA was reduced after PDT suggesting that PDT reduces chorioidal hyperpermeability seen in CSC and may work by a different mechanism than TLP [28].

Experimental studies have suggested that the main mechanism of action of verteporfin therapy is intravascular damage leading to thrombus formation and selective vascular occlusion. Direct endothelial cell damage probably results from the production of singlet oxygen and other free radicals with alteration of cell membranes [29]. However, other experimental studies have also described a chorioidal atrophy following standard PDT secondary to choroidal hypoperfusion [30]. For this reason and to prevent other ocular complications such as induction of CNV, chorioidal ischemia and RPE atrophy, modified parameters have been evaluated.

Along with the low-fluence PDT, other modified parameters have been studied in the treatment of CCSC such as the use of half the dose of verteporfin. The latter was evaluated by Chan et al. in 48 eyes. They found an improvement of BCVA and complete resolution of fluid after half dose verteporfin [31]. Unfortunately, in the study of Shinojima et al., a recurrent pigment epithelial detachment with or without retinal detachment was identified during the one-year follow-up of 5 out of their 17 patients after half-dose verteporfin for the treatment of CCSC [32].

Recently Reibaldi et al. demonstrated a complete resolution of subretinal fluid after low-fluence PDT for CCSC in 21 eyes (91%). In a second study, they described a significant improvement in macular sensitivity after PDT for CCSC with greater efficacy of low-fluence PDT in comparison to standard parameters [26,27].

However, even if many studies show very encouraging results with low-fluence PDT, long-term follow-up studies are lacking in literature.

In our study, the mean follow-up period was longer than 3.5 years (43.9 months). We found an improvement in visual acuity in 31 out of 38 eyes (81.5%).

Those results are very similar to those found in the recent study of Silva et al. In that study, 46 eyes had been treated with standard PDT for CCSC with a minimal follow-up period of 48 months (mean follow-up 56.8 months). They found an improvement in VA in 74% of eyes with a gain of line of 2 in LogMar scale [33]. The gain of line in our series is equal to 2.2 lines in the total group of 38 eyes. When we observed the group of patients with a minimal follow-up of three years (mean follow-up of 53.28 months) we found an improvement of VA of 2.3 lines (initial mean BCVA of 0.32 and final mean BCVA of 0.09) in 26 eyes.

Our initial mean VA was much higher than the one in Silva et al.’s study. This observation could suggest a more advanced disease and/or longer duration of disease in their population of patients than ours.

Resolution of subretinal fluid was achieved in 93.4% of cases in Silva et al. study at 48 months while we found a resolution of 94.7% of cases at last follow-up visit. No recurrences were noted in any of the patients during the study.

Five eyes had a stabilization of their vision. Two patients showed a small decrease in vision.
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Those patients had a high VA before treatment and a dry OCT after low-fluence PDT. Their symptoms disappeared and both patients claimed to have recovered an excellent subjective visual outcome.

Those 2 cases reveal one of the bias of the study. Indeed, the patients treated with a high VA before treatment cannot experience any more increase of their VA after treatment. However, those patients seem to feel a subjective benefit of the treatment that we cannot measure in terms of VA.

Two out of the five patients mentioned above in whom no improvement of VA was noted had a longer CCSC duration (3 years and 16 years before PDT treatment for the patients with stable visual acuity). Although these eyes showed resolution of subretinal fluid on OCT images, the visual acuity did not improve as predicted. This observation could suggest that an earlier treatment would result in a better final visual acuity. Indeed, studies that have been analyzing high resolution OCT images have reported the correlation between IS/OS line and visual acuity [34,35]. Long lasting retinal detachment causing damages to the photoreceptor outer segments may thus explain the poor visual outcome after a delayed treatment.

Since our study is the longest evaluating effects of low-fluence PDT in CCSC, an interesting finding was to follow central retinal thickness in time after treatment. We were able to collect those data in 21 eyes with a minimal follow-up of 24 months. Those results can show there is no statistical significant change between CRT performed just after low-fluence PDT and at the last visit in the group of patient with a minimal follow-up of 24 months. This indicates the absence of significant thinning of the retinal thickness in time in our patients. However, this study was not designed to evaluate CRT and further studies analyzing OCT findings more precisely should be needed.

One patient developed juxtafoveal CNV several years after his treatment. Low-fluence PDT had shown good results in this patient on OCT findings (performed at 3 months, 1 year and every year after the treatment) as well as FA (performed every year) and ICGA (performed before treatment, 1 year and 3 years after treatment). There are a few possibilities which could explain the presence of CNV in this case. A small neovascular activity could have been present before treatment and gone unnoticed on initial examinations. This neovascular complication might also have occurred during the natural course of disease [35]. Finally, it could have developed as a consequence of the PDT treatment.

Although PDT treatment was performed 4 years before the development of CNV, this complication can occur after a PDT treatment [24]. Therefore, the use of modified parameters such as low-fluence PDT has been presented as a possible safer option in the treatment of CCSC. For safety reasons, further studies evaluating the long-term effects of low-fluence PDT should be carried out.

This study has its shortcomings as it was not a prospective, randomized and controlled clinical study. Secondly, it was not designed to evaluate retinal sensitivity and choroidal response after treatment. More precise functional studies as electroretinography, micropereometry, EDI-OCT and contrast sensitivity should complete the evaluation of long-term effects of low-fluence PDT in the treatment of CCSC. However, these long-term results are very encouraging as good visual acuity and complete resolution of subretinal fluid seems to be maintained over time. Our results confirm indirect evidence suggesting that lower fluence PDT might be as beneficial as standard PDT in the treatment of CCSC, which already has diseased RPE and choriocapillaris [25,26].

In conclusion, this study is the first evaluating long-term effects of low-fluence PDT. Our results were comparable to the similar recent long-term study of Silva et al. evaluating standard PDT in the treatment of CCSC. In a condition where RPE is already damaged by the disease, it should be preferable to chose low-fluence parameters as they give the same results with a possible lower risk of complications.

Disclosure of interest
The authors declare that they have no conflict of interest concerning this article.

References


