Central Serous Chorioretinopathy Treatments: A Mini Review

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Key Words
Central serous chorioretinopathy · Laser treatment · Photodynamic therapy · Anti-vascular endothelial growth factor · Mineralocorticoid antagonists

Abstract
Central serous chorioretinopathy (CSC) is a retinal disorder that primarily affects young (20- to 50-year-old) white men, although it is seen occasionally in older patients and females. CSC is characterized by avascular focal leakage through the retinal pigment epithelium (RPE), resulting in serous detachment of the neurosensory retina. The course is usually self-limiting and in most cases resolves spontaneously within a 3-month period, with visual acuity usually recovering to 20/30 or better. However, chronic CSC may develop as a consequence of recurrences or persistent neurosensory detachment, and can result in progressive RPE atrophy and permanent visual loss. A primary involvement of the RPE and choroidal vasculature play a significant role in the pathogenesis of CSC and the current treatment options attempt to restore the functions of the RPE and the normal choroidal vasculature. The aim of the current review is to provide an overview of the current therapeutical approaches to CSC, including observation, laser treatment, photodynamic therapy with verteporfin, intravitreal anti-vascular endothelial growth factor therapy and the mineralocorticoid receptor antagonists.

Introduction
Central serous chorioretinopathy (CSC) is a condition characterized by a serous detachment of the neurosensory retina (SRD) and/or a detachment of the retinal pigment epithelium (RPE) at the posterior pole that typically affects young and middle-aged adults [1]. Although precise data on its prevalence are not available, CSC is rated as the fourth most frequent cause of retinopathy [2].

In its most common form, patients affected by CSC of recent onset complain of blurred vision with a relative central scotoma and metamorphopsia, possibly associated with dyschromatopsia, micropsia and a reduction in contrast sensitivity [1, 2]. Fluorescein angiography discloses the presence of a focal point of leakage under a serous neuroretinal detachment with dye diffusion in the form of a ‘smokestack’ pattern, but multiple leaking points may also be observed [3–5]. Indocyanine green (ICG) angiography allows the visualization of changes involving the deeper
choroidal vascularization and reveals the presence of a delayed initial filling of arteries and choriocapillaris in the early phase of the examination, and a remarkable dilation of the large choroidal vein in the following phases, confirming a status of choroidal hyperpermeability [6–8]. Optical coherence tomography is usually performed to better visualize the morphologic changes involving the single retinal layers and the alterations occurring in the RPE, and also to follow up the disease evolution [9–12]. In particular, deeper penetration with recent spectral-domain and swept-source optical coherence tomography has led to a more detailed evaluation of the alterations of the photoreceptor layer and of RPE changes, including the presence of pigment epithelium detachments, the presence of microrip, hypertrophy or atrophy of the RPE, and has especially confirmed the presence of the thickening of the deeper choroidal layers composed by the larger vessels and the thinning of the inner choroidal layers [13, 14].

Acute CSC usually resolves spontaneously within a few months with complete reabsorption of the fluid collection and visual acuity recovery close to premorbid values [15, 16]. A slight impairment in contrast sensitivity and color discrimination may be maintained without any resulting disability. Thus, in these cases simple observation appears the most appropriate approach [2].

A single episode of acute CSC may convert to multiple recurrences of SRD or result in chronic SRD with persistent fluid. In the first condition, subretinal fluid collection may reappear in 30–50% of cases within 12 months of the first episode and resolve again spontaneously [17]; in studies with a long follow-up period, SRD reoccurred in 15–50% of the cases [17–20]. In eyes with chronic SRD, a longer persistence of fluid collection is detected and is associated with widespread RPE decompensation. Although a consensual definition of chronic CSC (otherwise and commonly termed diffuse retinal pigment epitheliopathy or DRPE) has not been achieved, most authors define chronicity as persistent fluid collection for at least 3–6 months [21]. Recurrent and chronic CSC are both linked to a less favorable visual prognosis. The persistent presence of the subretinal fluid associated with a progressive deterioration of the RPE functions may be a cause of vision loss secondary to progressive retinal damage [2, 17, 18]. Although a clear and definitive comprehension of the pathophysiology of CSC is not completely understood, several investigations convey a hypothesis and results that suggest a primary involvement of the RPE and choroidal vascularization [21].

RPE plays a significant role in the integrity of the barrier function. In acute CSC, the point of leakage observed on the fluorescein angiography was thought to be the site of fluid flow from the choroidal compartment to the subretinal space. However, some authors demonstrated recently that in the site of the focal RPE defect an outflow from the subretinal compartment towards the choroidal space can be observed [22]. In chronic CSC, a diffuse alteration of the RPE – as evidenced in the fundus fluorescein angiography and in the fundus autofluorescence analysis – may explain the impairment of the barrier and the pumping functions responsible for the chronic fluid collection. The etiopathogenetic path that leads to a loss in the activity of RPE functions has not yet been fully clarified. The RPE could be susceptible to a loss of activity as a result of an increase in hydrostatic pressure in the choroidal compartment or in response to a negative effect of ischemic origin, or due to inflammatory or hormonal influences, as has been alternatively hypothesized.

Choroidal circulation plays a significant role in the pathogenesis of CSC. An increased hyperpermeability of the choroidal laminae is easily observed in the ICG examination and it is thought to be a consequence of the phenomena of stasis, inflammation or ischemia [15]. The corresponding increase in hydrostatic pressure within the choroidal compartment could overwhelm the pump functions of the RPE and, in accordance with simple mechanical theory, lead to a progressive fluid accumulation in the subretinal space. The causes responsible for the increased vascular permeability remain to be determined. The self-regulating mechanisms of the vascular choroidal circulation in CSC appear to be influenced by the levels and chemical activities of steroid molecules, catecholamines and sympathomimetic agents. The complexity of the mechanisms at the origin of the CSC and the heterogeneous expression of its clinical manifestations mirror the variability in the current therapeutic management of this retinal disorder.

The aim of the current review is to provide an overview on the current treatment options for acute and chronic CSC, including observation, retinal laser treatment, photodynamic therapy (PDT) with verteporfin, intravitreal anti-vascular endothelial growth factor (VEGF) therapy, and the mineralocorticoid receptor (MR) antagonists.

**Treatment Options**

**Observation**

Taking into consideration the self-limiting and favorable course of the first episodes of acute CSC in most patients, a simple observatory approach is advised. The pa-
tient should be monitored periodically to observe the progressive resolution of the neurosensory detachment that normally takes place within a period of 3 months [15, 23]. Patients receiving corticosteroid therapy with any route of administration, including oral consumption, intravenous administration, inhalation, intranasal or epidermal administration, should be advised on the potential benefit of the discontinuation of the steroid therapy [24]. In addition, obstructive sleep apnea, the use of 5-phosphodiesterase inhibitors or sympathomimetic drugs, pregnancy, signs or symptoms related to Cushing’s syndrome and the presence of a ‘type A’ personality pattern should be determined in the general clinical assessment because of the possible associations reported in some case series [25–27].

**Laser Photocoagulation**

Focal laser photocoagulation delivery to the leakage site has become the most common treatment in current clinical practice for acute CSC. The treatment attempts to produce a ‘sealing’ of the RPE defect as identified through fluorescein angiography. An additional effect of the retinal laser photocoagulation is a promoting effect on the pump function of the RPE through stimulation of the closer RPE cells [20, 28, 29].

Controlled studies comparing laser photocoagulation to simple observation or sham laser treatment provided evidence of the beneficial effects of laser treatment on the time for resolution of the neurosensory retinal detachment (NSD). In detail, patients receiving laser treatment showed a faster flattening of the NSD measured in a mean period of 8–10 weeks [28, 30]. Despite this meaningful anatomical improvement, the laser treatment appeared less effective in achieving a significant change in visual acuity. Similarly, the laser photocoagulation seems not to be able to reduce the recurrence rate of new episodes of active CSC [20]. In studies with a long-term follow-up in the range of 58–108 months and comparing argon laser treatment with observation, no significant reduction in the mean number of recurrences of NSD was found in the treated group. Only the study by Burumcek et al. [4] reports a demonstrated lack of recurrence in the laser photocoagulation group, which compared with seven eyes in the control group that showed one or more recurrences during the mean follow-up period of 4.8 years [16, 20, 28, 30].

The complication rate following laser treatment is generally low. Choroidal neovascularization may occur in the site of laser application in less than 10% of the treated cases. It usually has an extrafoveal location and should be taken into consideration during disease monitoring [20]. The delivery of laser spot in the juxtafoveal area should consider the residual paracentral scotoma which could negatively affect reading ability [16, 20].

Although clear recommendations cannot be drawn, laser treatment should be considered to shorten symptom duration relative to the presence of the NSD and based on the patient’s condition, taking into account working needs and personal demands.

**Subthreshold Retinal Laser Treatment**

In an attempt to avoid morphofunctional alterations secondary to retinal photocoagulation – especially paracentral scotoma, scar expansion and CNV occurrence at the site of the laser spot – some authors explored the effects of laser application in a subthreshold setting in the treatment of acute and chronic CSC. Histological studies have indicated that when applying short-duration diode laser pulses the RPE is almost solely affected, with little histopathological effect on the inner retina [31].

Application of subthreshold diode laser treatment (810 nm) was first described by Bandello et al. [31]. Five patients with chronic CSC with a disease duration lasting more than 3 months were initially included and treated with multiple laser spots applied over and adjacent to the area of RPE leakage or decompensation. Within 1 month all patients had experienced a complete resolution of their NSD.

Verma et al. [32] compared the effects of a micropulse diode laser (810 nm) with standard argon laser photocoagulation in a randomized clinical trial. The study considered patients with acute CSC, with a symptom duration of less than 8 days and with a single focal leakage site. Based on a statistically significant difference in the time for visual acuity recovery, a final better contrast sensitivity and the absence of a paracentral scotoma in the site of laser application (3/15 eyes receiving argon laser treatment), the micropulse diode laser was suggested as a better alternative to argon green laser in patients with CSC.

Additional evidence supporting the beneficial effects on the time for resolution of the NSD, contrast sensitivity and the absence of retinal damaging of the subthreshold laser treatment in CSC has been provided in several case series. However, the comparison of results between the different investigations is awkward, mainly due to the heterogeneous inclusion criteria, the laser setting and the area of application of the laser spots [33–43]. The studies consider acute CSC forms with symptom durations lasting a few days or less than 1 month as well as chronic forms with a duration range of 3–6 months. Additional
variability is found in the frequency (810 nm vs. yellow 577 nm) and setting of the laser device (diameter, power, duty cycle and pulse duration), and in the determination of 'no burn'. Finally, the distribution of the laser spots is greatly variable. The application of laser spots may be targeted to the single leakage points, the area of the NSD with foveal sparing (810 nm), both the NSD and leakage points, the foveal area and the normal retina surrounding the NSD (yellow 577 nm), the area of diffuse leakage, or the single leaking site as evidenced on ICG just after the dye infusion. There is clear evidence that this method of treatment needs to be investigated in prospective, randomized, controlled trials, with well-established inclusion criteria and treatment strategies.

**PDT with Verteporfin**

The possibility of a new means of application of PDT with verteporfin in the treatment of CSC was initially described by Battaglia Parodi et al. [44] in a single case report. The authors suggested a possible direct action on the choriocapillaris endothelium along with the choriocapillaris occlusion that is able to achieve both a blood flow stasis and a reduction of vascular permeability. The combination of these factors may lead to a decrease in the fluid passage toward the retina. In this way, PDT with verteporfin could act on the pathogenic mechanism that would see the involvement of the chorioidal vascular hyperpermeability.

The first case series with a short-term follow-up conveyed similar results. Yannuzzi et al. [45] reported outcomes obtained from 20 eyes of 15 patients who received standard PDT for chronic CSC with laser treatment targeting the area of chorioidal hyperpermeability recognized by ICG angiography. A complete resolution of NSD was detected in 12 patients (60%) and it was associated with a vision improvement in six eyes. PDT was initially applied for acute CSC by Ober et al. [46] in 9 eyes to treat focal RPE leaks recognized on fluorescein angiography. The neurosensory detachment and fluorescein leakage resolved in all patients within 1 month and a statistically significant improvement in mean best-corrected visual acuity (BCVA) was registered at the 6-month evaluations, with no patient losing vision or experiencing side effects.

Following this, several other investigations provided support to these promising results. The hypothesis that causal intervention on increased vascular permeability could lead to a faster resolution of the NSD with an associated more rapid visual recovery with fewer recurrences was formed [47, 48]. However, diffuse application of PDT for CSC led to evidence of adverse events which included pigmenary changes in the treated area, RPE atrophy, choriocapillaris nonperfusion and iatrogenic choroidal neovascularization [49, 50].

PDT was initially administered according to the TAP protocol with an applied energy density of 50 mJ/cm² over 83 s after intravenous injection of 6 mg/m² of verteporfin over 10 min. In order to minimize the adverse events secondary to standard PDT, several investigators tried to change the PDT treatment setting parameters by modifying fluence, laser treatment times, the verteporfin dose or the time between verteporfin injection and laser delivery [48, 51, 52].

In a randomized clinical trial, Chan et al. [52] compared the efficacy of half-dose PDT with placebo in acute CSC. Sixty-three eyes that had CSC for 3 months were randomized to ICG-guided half-dose PDT (3 mg/m²) or to placebo. At 12 months, 94.9% of the PDT group compared to 57.9% of the placebo group showed complete resolution of the NSD (p = 0.001) and, similarly, the BCVA was significantly better in the PDT group, which also contained the greater number of eyes with stable or improved BCVA (100% in the PDT group vs. 78.9% in the placebo group).

Half-dose PDT was also compared with focal laser photocoagulation by Lim et al. [48] in a prospective study. In a cohort of 26 eyes, 12 eyes received focal laser treatment and 14 eyes underwent half-dose PDT treatment. After 1 month, a greater proportion of eyes in the PDT group showed a complete absorption of subretinal fluid compared with the laser group (p = 0.022). No significant variation was measured in visual acuity or in the parameters of multifocal electoretinography between the two groups during the 6-month follow-up period.

In a randomized clinical trial recruiting 131 patients, Zhao et al. [53] compared the efficacy and safety of a 50% dose of PDT with the efficacy and safety of a 30% dose for acute CSC. During the 1-year follow-up, half-dose PDT was superior to 30% dose PDT in terms of resolution of subretinal fluid, fluorescein angiography leakage, recurrence of NSD and fluorescein leakage. No BCVA difference was measured between the two groups, and no ocular side effects were registered in the study.

Standard-fluence PDT was also compared with half-fluence PDT in chronic CSC in a prospective nonrandomized clinical trial by Reibaldi et al. [54] in a cohort of 42 eyes during 1 year of follow-up. No difference was measured between the two groups with regard to BCVA improvement and the proportion of eyes with complete subretinal fluid reabsorption. A statistically significant greater proportion of moderate choriocapillaris nonper-
fusion was seen in 8 eyes receiving standard-fluence PDT compared with no cases in the group receiving half-fluence.

There is no clear evidence for whether or not a specific setting of the PDT protocol has to be recommended and, moreover, the studies’ outcomes refer to a relatively short-term follow-up. Many aspects remain to be determined, including the effects of PDT on chorioretinal atrophy, the role of PDT for patients showing no or minimal choroidal hyperpermeability, the action of PDT on the rate of recurrences and the cumulative effect of repeated treatments [52–57].

Mineralocorticoid Antagonists

The introduction of drugs such as spironolactone and eplerenone in the treatment of CSC has been founded on the base of a pathogenetic mechanism involving the aldosterone/MR and the choroidal hyperpermeability [21]. It is well known that an excess of endogenous (cortisol) or exogenous glucocorticoids is associated with CSC and that glucocorticoids also show to some extent an affinity for the MR. The mechanism linking the subretinal fluid accumulation and the activity of glucocorticoids seems to involve the overactivation of the ocular MR through an overexpression of the MR or an increased stimulation. Studies performed on animal models have demonstrated that, following an intravitreal injection of aldosterone or high dose of glucocorticoid, an increased expression of ion and water channels on the outer limiting membrane can be observed [58]. Similar observations have been confirmed on human Müller glial cell lines [59]. As a consequence of intravitreal aldosterone injection, the accumulation of fluid in the subretinal space could be observed and was associated with vasodilation and leakage of the choroidal vasculature and increased choroidal thickness.

Spironolactone and eplerenone are currently in use for the treatment of primary aldosteronism and hypertension, respectively. They differ in terms of binding affinity for the MR, which is higher for spironolactone. On the other hand, eplerenone shows an increased selectivity and fewer side effects secondary to the activation of progesterone receptors, including gynecomastia, erectile dysfunction and menstrual irregularities [60].

Information regarding the effects of spironolactone in the treatment of CSC derives from an uncontrolled, prospective case series [61] and a randomized, controlled crossover study [62]. In the study by Herold et al. [61], 18 consecutive patients with CSC lasting for more than 3 months were treated with 25 mg of spironolactone twice daily for up to 12 weeks. The subretinal fluid decreased from 219 to 100 μm and the total central retinal thickness reduced from 405 to 287 μm. In parallel, a statistically significant improvement in the BCVA from the baseline value of 0.32 to 0.20 could be registered.

Bousquet et al. [62] designed a prospective, randomized, double-blinded, placebo-controlled crossover study which enrolled a total of 16 patients with CSC lasting for 3 months or more. The patients were randomized to receive either spironolactone 50 mg or placebo for 1 month; following a washout period of 1 week, each patient crossed over to the other treatment arm for an additional 30 days. A statistically significant reduction in NSD was obtained in the group receiving spironolactone in comparison with the placebo group both during the first month of treatment and after the crossover. Similarly, a significant reduction in the subfoveal choroidal thickness was detected in the active-treatment group. No significant difference was noted in BCVA variation.

The short follow-up period in both studies prevented evaluation of the efficacy of the treatment in terms of complete resolution of the NSD, which was observed in just 25% of cases in the study by Herold et al. [61] and was not evaluated in the study by Bousquet et al. [62].

Also, the efficacy of eplerenone for the treatment of chronic CSC was investigated in some case series, each with a short-term follow-up [63–67]. Two recent retrospective studies provided evidence of beneficial effects of oral eplerenone on BCVA improvement and in the reduction of the height of the NSD. Salz et al. [63] reported a statistically significant improvement from the baseline BCVA of 0.40 LogMAR to 0.27 at 3 months and a significant mean reduction of the subretinal fluid by 100 μm in 14 patients. Only a trend in the mean reduction of the choroidal thickness was correspondingly observed. Excluding the analysis of choroidal thickness, similar results were achieved by Singh et al. [64] in a retrospective analysis carried out in 13 patients. Both studies corroborated the outcomes of a previous prospective study with 3 months of follow-up performed by Bousquet et al. [67] in a similar small population study. At 3 months, compared with baseline values, the subretinal fluid had significantly decreased and the BCVA had significantly improved. Considering all the studies, a complete NSD resolution was detected in 35–67% of cases and no significant adverse events were registered. The studies differed with regard to dose administration of the oral eplerenone; in detail, the study by Singh et al. [64] employed 25 or 50 mg per day, whereas Bousquet et al. [67] and Salz et al. [63] assigned 25 g of eplerenone per day during the first week followed by 50 mg daily until the 3-month examination.
The preliminary results available in the current literature support the use of MR antagonists in the treatment of chronic CSC. However, given the absence of randomized, controlled studies with a long-term follow-up, no formal recommendation can be drawn on the use of MR antagonists in the management of chronic CSC.

Anti-VEGF Therapy

Anti-VEGF drugs have been employed in the treatment of acute and chronic CSC with the aim of reducing choroidal vascular hyperpermeability, even in the absence of clear evidence of an increased intraocular concentration of VEGF levels [68]. Numerous small uncontrolled interventional case series and a few randomized clinical trials have provided some evidence of the efficacy of anti-VEGF therapy taking into consideration the BCVA improvement and NSD resolution. Chung et al. [69] evaluated the efficacy of bevacizumab for acute or chronic CSC in a recent meta-analysis. The authors concluded that the paucity of large randomized clinical trials, the remarkable clinical heterogeneity of the sample studies and the short-term follow-up periods prevented a clear identification of the positive effect of intravitreal bevacizumab in CSC. Bae et al. [70, 71] carried out a randomized, controlled trial comparing ranibizumab with half-fluence PDT in chronic CSC in a cohort of 32 patients with 1 year of follow-up. The authors demonstrated the overall superiority of PDT compared with ranibizumab considering the percentage of patients with complete resolution of the subretinal fluid (88.9 vs. 12.5%) and the reduction in choroidal hyperpermeability. Given the lack of large randomized, controlled trials with long-term follow-up clearly demonstrating the positive effects of anti-VEGF therapy for CSC, no specific recommendation may be suggested for the management of CSC.

Other Treatments

Many others drugs, including glucocorticoids antagonists such as mifepristone, ketoconazole, rifampicin, finasteride or methotrexate, melatonin, oral acetazolamide, aspirin, or physical treatments such as transpupillary thermotherapy, have been studied in small case series with short-term follow-up periods suggesting some evidence of efficacy in the treatment of CSC. Further investigations are warranted to better understand the precise role of these treatment modalities in the therapeutic approach to CSC.

Acknowledgements

The contribution of the Fondazione Bietti in this work was supported by the Ministry of Health and Fondazione Roma.

Disclosure Statement

F.B. is an advisory board member for Allergan, Novartis Pharmaceuticals Corporation, Farmila-Thea, Bayer Schering Pharma, Pfizer, Alcon, Bausch and Lomb, Genentech, Alimera Sciences, Sanofi Aventis and Thrombogenics. P.I. is a consultant for Novartis Pharmaceutical Corporation (Switzerland). M.B.P. is a consultant for Bayer Schering Pharma. B.F. has no proprietary/financial interest to declare.

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