Eye (2019) 33:1035–1043
https://doi.org/10.1038/s41433-019-0381-7

The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

Non-resolving, recurrent and chronic central serous chorioretinopathy: available treatment options

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Received: 9 June 2018 / Revised: 30 January 2019 / Accepted: 10 February 2019 / Published online: 1 March 2019

Abstract

Central serous chorioretinopathy is one of the most frequent causes of vision reduction among middle-aged men. This disease usually has a self-limiting course, but sometimes it lasts more than 4–6 months or a second episode follows a complete resolution of the first one. Nevertheless, to date no consensus exists about the duration threshold and therapy protocols for these non-resolving central serous chorioretinopathy. Treatment as half-dose and half-fluence photodynamic therapy, subthreshold micropulse laser treatment, mineralocorticoid receptor antagonists, intravitreal anti-angiogenic drugs, transpupillary thermal therapy, anti-androgenic drugs, methotrexate, Rifampicin and melatonin are described in this review. Complications are very uncommon but end-point results like central macular thickness reduction and best-corrected visual acuity improvement are difficult to compare among different therapeutic modalities due to different duration of follow-up and lack of homogeneity in patient recruitment. The aim of this review is focusing on treatment modalities for these chronic forms with comprehensive recent management updates according to latest clinical trial results.

Introduction

Central serous chorioretinopathy (CSCR) is characterized by a detachment of the neurosensory retina at the macula, with accumulation of serous fluid between photoreceptor segments and the retinal pigment epithelium (RPE).

CSCR used to be classified in acute form, a self-limiting disease lasting more than 4 or 6 months, and chronic form, lasting more. Nevertheless, the classification relying only on temporal criteria seems too simplistic.

Daruich et al. suggested a newer classification (illustrated below) [1]:

- Non-resolving CSCR (or persistent): a CSCR characterized by a neurosensory retinal detachment lasting >4 months after onset of the following symptoms: blurred vision, central scotoma, metamorphopsia, dyschromatopsia, hypermetropia and micropsia.
- Recurrent CSCR: an episode of acute CSCR following a previous episode with a complete resolution of neurosensory retinal detachment.
- Chronic CSCR (formerly named diffuse retinal epitheliopathy): a chronic chorioretinopathy with a widespread track of RPE atrophy with or without neurosensory retinal detachment.
- Inactive CSCR: patients with history of CSCR but without any sign of CSCR at the evaluation time.

Non-resolving, recurrent, and chronic CSCR forms often affect middle-aged men, having a huge impact on working-day lost; nevertheless, to date no gold standard therapy is available for these diseases [2], and our intent is to review the existing treatment options of these forms.

Incidence

The incidence of acute CSCR is approximately six times higher in men (9.9 per 100,000) than in women (1.7 per 100,000), with an average age between 39 and 51 years [3, 4]. CSCR especially affects Western European descent and Asian patients [5]. The prevalence of CSCR could have been under-estimated, in fact examining relatives or contralateral eyes of affected patients showed the presence of extramacular serous detachment [6, 7]. Generally, CSCR

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resolves in 3–4 months, nevertheless about 15% of patients develops a chronic form or non-resolving CSCR [8]. This kind of patients are older compared to ones affected by acute CSCR [9, 10].

Pathophysiology

During past years, a large variety of risk factors have been reported in CSCR pathophysiology leading to the development of new treatment options: cadherin 5 single-nucleotide polymorphism or complement factor H polymorphism [11, 12], cardiovascular disease and hypertension [13], endogenous corticosteroids [14], exogenous corticosteroids [2], type A personality [15], gastro-oesophageal reflux [16] and shift work [17, 18]. Instead, the role of sleep obstructive apnoea needs to be clarified [19].

According to recent theories, an increased permeability of choroidal vasculature overcomes the RPE barrier function, causing sub-retinal fluid (SRF) accumulation and retinal pigment epithelial detachment, but the exact responsible mechanism has not been fully elucidated. For these reasons, CSCR could be considered a different manifestation of a common pathologic process, named pachychoroid disease spectrum [20]. This novel concept should include other several diseases, as pachychoroid pigment epitheliopathy, pachychoroid neovasculopathy, polypoidal choroidal vasculopathy/aneurysmal type 1 neovascularization, focal choroidal excavation and peripapillary pachychoroid syndrome [21-24]. In fact, these different entities have common features as focal or diffuse choroidal thickening, choriocapillaris thinning, and an hyperpermeability of dilated choroidal vessels (named pachyvessels) [20].

Imaging

In chronic CSCR forms, fluorescein angiography (FA) shows multiple RPE leaks visible in mild and late phases and it used to be the gold standard for diagnosis [25].

Nevertheless, today optical coherence tomography (OCT) combined with fundus autofluorescence (FAF) can lead to a more accurate diagnosis compared to FA alone, reducing also adverse effect being both non-invasive exams. In particular, OCT can show choroidal thickening and pigment epithelial detachment (detectable also in acute CSCR), areas of RPE atrophy and RPE hypertrophy (typical of chronic CSCR forms) [26-28]. Moreover, there are fluid accumulation and morphological alteration in neuronal layers, like intra-retinal hyper-reflective spots, usually progressing from inner to outer retinal layers and correlating with worse final visual acuity [29]. Furthermore, OCT angiography shows choroidal neovascularization (CNV) in chronic CSCR better than other imaging techniques, allowing early and so more effective treatments. In particular, CNV is highlighted as small undulating RPE detachment on B-Scan [30].

Finally, the pathognomonic FAF pattern occurring in chronic CSCR of multiple oblong hypoautofluorescent descending tracks, often starting at the macula or at the optic disc, encircled by a thin contour of hyperautofluorescence is quite out-dated [31]. Recently, Zola et al. [32], assessing the evolution of FAF in chronic CSCR, reported different FAF patterns that can be observed in this disease. In particular, Zola described: granular hypoautofluorescence (the most frequent), confluent hypoautofluorescence, punctate hyperautofluorescence, and diffuse hyperautofluorescence (the earliest, occurring about 4 months after the first SRF development). Changes between FAF patterns are slow and occur only in 25% of patients during 3 years of follow-up. Furthermore, there is a correlation between altered FAF areas and retina sensitivity (RS) quantified by microperimetry: hypoautofluorescence areas correspond to decreased RS, hyperautofluorescence ones to both decreased or normal RS, absence of autofluorescence to absolute scotoma [33]. Recent research using enhanced-depth OCT and swept-source OCT confirmed a pathological choroidal thickening with dilation of choroidal vessels in CSCR, corroborating the novel concept of pachychoroid disease [34].

Treatment options

Treatment options are listed from the most widely used, supported by largest clinical trial, to ones still at an investigative level.

Verteporfirin photodynamic therapy (PDT)

PDT is generally recommended for chronic CSCR, releasing free radicals that damage endothelium, could reduce the choroidal vasculature hyperpermeability and extravascular leakage, provoking a long-term vascular remodeling. PDT led to a significant best-corrected visual acuity (BCVA) improvement and SRF resolution in 70–100% of patients [35, 38]. Furthermore, patients could experience an early BCVA reduction immediately after PDT treatment, but it is a transient effect, not compromising final visual improvement [39].

Nevertheless, owing to reported complications of choriocapillaris hypoperfusion, choroidal infarction, and CNV development [40], PDT parameters, originally used for neovascular age-related macular disease, have been modified to improve safety, reducing the fluency or the dose of verteporfirin. Both of strategies have shown to be safe and

effective in large retrospective studies with sufficient follow-up period [41-44].

In particular, PDT reduces choroidal thickness, leaving choriocapillaris unchanged with a therapeutic effect exerts on dilated choroidal vessels [45, 46].

Notwithstanding the above, it is unclear which PDT modality (half-dose or half-fluency) is better. Two studies showed that both modalities have the same efficacy in terms of gain of BCVA, central macular thickness (CMT) reduction and SRF resolution [47, 48]. Instead, a review by Nicolo et al., [49] reported that half-dose PDT induced faster and more lasting results.

Long-term studies should allow adjustment of PDT parameters to maximize the efficacy and minimize the rate of recurrences and adverse effects.

Laser treatments

Supra-threshold laser photocoagulation delivery to the leakage site is a valid treatment option in CSCR. It can debride the RPE at the leakage site allowing an ingrowth of the surrounding RPE and accelerating SRF resolution [50].

Nevertheless, laser photocoagulation is not feasible for subfoveal detachment due to scar and subsequent central scotoma and does not reduce the recurrence rate of neurosensory retinal detachment [51-53].

Subthreshold micropulse laser (SML) treatment, instead, destroys only RPE cells generating a high peak temperature around RPE intracellular melanosomes leading to cellular membrane rupture but avoiding any damage to photoreceptors and preventing scars. Therefore, SML can produce the same biological effect of suprathreshold laser with fewer side effects [54, 55].

Scholz et al. [56] reviewed 12 studies including 191 patients about SML treatment (both 810 and 577 nm) of CSCR lasting >4 months. In all, 79.6% of 191 patients showed a reduction of CMT and 63.6% a complete resolution of SRF. Two studies included a control group of untreated patients where CMT reduction was detected in 39% and a complete SRF resolution only in 8%. Four studies had a control group treated with verteporfirin PDT (both half-fluence and half-dose); CMT reduction was seen in 64% of patients and a complete resolution in 46%. Finally, no adverse effect, like CNV and scar formation, occurred.

Another review by Wood et al. [57] including 398 patients treated with SML, with a median follow-up of 12 months, showed a CMT decrement of 80 µm and a BCVA increase of 9 letter on average, without any adverse effects.

The 577 nm SML offers the advantage that is absorbed minimally by xanthophyll, a pigment located in the inner and outer plexiform layers of the macula, so treatments near the fovea are relatively safe [58]. A prospective study by Arsan et al. [59] evaluated the efficacy of 577 nm SML in 39 patients with CSCR lasting >3 months. The median follow-up time was 18 months. CMT decreased from 369 to 250 µm and BCVA increased significantly ($p < 0.01$ for all parameters).

Finally, both half-fluence/half-dose PDT and SML seem to be effective treatments for chronic CSCR, but which should be the first choice is not clear.

Ntomoka et al. [60] showed that SML is superior in terms of efficacy to PDT (visual acuity improvement 0.12 vs. −0.02 ($p = 0.039$), SRF resolution 59% vs. 21.7%, CMT reduction 85.5 µm vs. 24.47 µm ($p = 0.02$), respectively, 6 months after treatment). Nevertheless, these outcomes have not been confirmed by PLACE trial results recently published by van Dijk et al. [61]; in particular, a higher rate of SRF resolution after half-dose PDT treatment compared to SML treatment has been shown, both at the first post-treatment evaluation at 6–8 weeks (51.2% vs. 13.8%, $p < 0.001$) and after 8 months (67.2% vs. 28.8%, $p < 0.001$), despite the improvement in vision-related quality of life being similar for both treatments. Some authors speculated that the limited SML efficacy compared to PDT is due to the SML limited effect on reducing choroidal thickness [20].

According to the PACORES (Pan-American Collaborative Retina Study) Group, SML is cheaper and could be considered a valid alternative if PDT is not available [62].

Mineralocorticoid receptor (MR) antagonists

The presence of MR in the sensory retina, the RPE, and the choroid has been proven by some studies on monkeys, humans and rats [63, 65].

In particular, MR receptor pathway activation causes choroidal vasodilation and leakage, due to upregulation of the vasodilator potassium channel KCa2.3 (calcium-dependent channel) and smooth muscle cells relaxation in the choroidal vasculature [66]. These evidences have also been supported by ophthalmologic findings within patient with primary hyperaldosteronism [67].

For these reasons, CSCR treatment with MR antagonists could have a potential role, but clinical results are controversial. For example, Ghadiali et al. [68] treated 23 eyes with chronic CSCR (defined as persistence of SRF for >6 months) with either spironolactone or eplerenone for 12 months. The therapy improved BCVA at 12 months but CMT and SRF did not show any significant reduction. Both MR antagonists have been well tolerated.

Instead, Cakir et al. [69] published a retrospective study about 24 patients with CSCR resistant to conventional therapy over at least 4 months. An initial dose of 25 mg oral eplerenone was administered for a week, followed by a 50 mg dose daily, if no adverse effect was reported. In all, 29% of patients experienced a complete SRF resolution

after a median of 106 days, 33% a transient SRF reduction and 25% failed to respond. Also, 13% of patients reported adverse effect so treatment was stopped (in particular, hyperkalaemia, myotonia, bowel irritation). At the beginning, 6 patients on 24 showed a widespread RPE atrophy on OCT and they were classified as chronic atrophic CSCR. This subgroup did not show a visual acuity improvement; on the contrary, remaining patients' BCVA improved similar to Ghadiali's study.

Daruich et al. [70] treated 54 eyes from 42 patients with non-resolving CSCR with oral eplerenone or spironolactone with a similar dose of the previous study by Cakir. CMT decreased at 1, 3 and 6 months after treatment initiation and BCVA significantly improved at 6 months.

It is noteworthy patient's subgroup classification: recurrent CSCR, persistent CSCR, and persistent with epitheliopathy. In the latter, the kinetic of resolution was slower compared to the others.

A recent prospective, randomized study by Schwartz et al. [71] showed no superiority of eplerenone to placebo. In this study, 17 patients have been treated with eplerenone 50 mg/day or placebo for 3 months, followed by 3 months of follow-up.

Instead another prospective, randomized study by Rahimy et al. [72], which enrolled 15 patients treated with 50 mg/day or placebo, showed a significant BCVA improvement and CMT reduction of the eplerenone treatment arm compared to placebo group.

In conclusion, clinical study testing the role of MR antagonist in the treatment of chronic CSCR forms reported different results. A recent genetic study by van Dijk et al. may partly explain these differences: carriers of different MR haplotypes may respond differently to MR antagonists [73].

Further clinical study should stratify patients in different subgroups according to their MR haplotypes to show different efficacy results, allowing tailored treatment approach.

Finally, these studies should also compare MR antagonist treatment vs. SML or PDT, to date the most effective ones, as on-going SPECT trial (NCT03079141).

Anti-vascular endothelial growth factor (anti-VEGF) agents

Although in CSCR there is not an increment of ocular VEGF levels [74], intravitreal anti-VEGF agent injections could have a potential therapeutic role; in particular, they should reduce hyperpermeability and congestion of choroidal vessels [5]. For this reason, several clinical studies have been carried out but result are controversial [75]. A recent meta-analysis investigated anti-VEGF treatment's role showing a significant reduction of CMT at 1, 6 and 12 months of follow-up compared to observation but not a BCVA improvement [76]. Therefore anti-VEGF treatment could be an alternative treatment but cost/benefit is not proven and half-fluence PDT seems superior to it [43].

Instead, anti-VEGF agents have an important role in treating CNV secondary to chronic CSCR [77]. This complication develops in 4–8% of patients with chronic CSCR [78, 52, 79], and recently, Peiretti et al. [80] reported a similar efficacy of full-fluence PDT and intravitreal anti-VEGF agents for its treatment.

Nevertheless, larger long-term randomized controlled studies are needed before clinical application of this kind of treatments would be possible.

Transpupillary thermal therapy (TTT)

TTT could have a therapeutic role in chronic CSCR, because the diode laser has a wavelength of 810 nm, mainly absorbed in the choroid, allowing an effective treatment of pachychoroid disease.

Shukla et al. treated 39 eyes with chronic CSCR (lasting >4 months), with 0.5 mm spot for 1 min, mean power of 90 W. Within 3 months, SRF resolution has been obtained in 96% of treated eyes and BCVA increased in 92%. One case developed CNV [81].

Hussain et al. conducted a prospective study on 14 eyes with chronic CSCR (lasting >3 months) with TTT using different settings: mean spot size 2.2 mm, mean power 156.4 W, and exposure 30–45 s. Three months after treatment, 78.6% of eyes showed a complete SRF resolution ($p = 0.001$) and 52.7% had ≥3 lines of BCVA improvement on Snellen's chart [82].

Instead, Mathur et al. used a different protocol on 25 patients, using spot of 1.2 mm, with power of 120–200 mW and 2–3 s of exposure. After 2 months of treatment, out of 25 patients, 52% had SRF resolution and BCVA improvement ≥2 lines, 42% showed only SRF resolution and 8% had persistent SRF [83].

Manayath et al. published a retrospective study about 10 eyes with a mean CSCR duration of 20 months treated with TTT. Power was reduced by 60% from threshold with an exposure of 60 s. Treatment was repeated if persistent SRF was noted at 1 month of follow-up. In all, 50% of eyes showed an improvement ≥3 lines and 30% up to lines [84].

Recently, same authors compared TTT vs. half-fluence PDT in a non-randomized prospective trial on 42 patients, 20 treated with PDT and 22 with TTT. At 6 months of follow-up, both groups showed a significant CMT reduction ($p = 0.001$) and a similar BCVA improvement. Nevertheless, patients in TTT group required more treatment sittings and longer time for SRF resolution [85].

TTT could be a useful and cost-effective alternative in chronic CSCR treatment, but larger randomized controlled trials are needed to address issues about TTT parameters, long-term efficacy and safety.

Anti-androgenic drugs

An increased testosterone level has been involved in the pathogenesis of CSCR, so an anti-androgenic drugs such as finasteride, an inhibitor of 5-alfa-reductase, could have a potential therapeutic role [86-88]. In particular, this drug prevents testosterone from changing to dihydrotestosterone, which binds the androgen receptor with a greater affinity [89].

To date, only two studies have investigated this potential treatment.

Forooghian et al. [90] recruited 5 male patients with SRF lasting at least 3 months or a recurrence of SRF in the past 3 months and treated them with 5 mg of finasteride daily for 3 months with another 3 months of follow-up. BCVA remained stable. SRF and CMT declined until assumption and rose after discontinuation, but at 6 months, parameters were inferior compared to the baseline ones. Only one patient had a complete resolution of SRF at the end of the study.

Moisseiev et al. [91] recruited 23 patients, both male and female, with SRF or symptoms of CSCR for at least 3 months. Twenty-nine eyes (so 6 patients with bilateral CSCR) have been treated as the previous study but with a longer follow-up of 6 months after the discontinuation of the drug. A significant SRF reduction was observed, with a 79.5% rate of complete resolution. No adverse effect was noted, also in female patients. Thanks to the impressive results and safety profile, these researchers suggested a treatment protocol: prescribe finasteride as first-line therapy in chronic CSCR forms for 3 months, then if it succeeds follow-up the patient, treating any recurrence with finasteride again or PDT, instead if it fails they suggested to switch immediately to PDT or other alternative treatment. Nevertheless, large clinical trials are needed to use finasteride in current clinical practice.

Methotrexate (MTX)

MTX is an antimetabolic agent with an immunosuppressive effect used for treating various inflammatory disease. Beyond this action, it is also an anti-angiogenic drug, so it could have a potential therapeutic role [92, 93].

In particular, Kurup et al. treated [94] 9 patients with an average SRF persistence of 2 years with a weekly dose of 7.5 oral MTX along with 1 mg of folic acid daily for 12 weeks. They achieved a significant improvement of BCVA and a reduction of CMT in 83% of patients, without any toxic effect. Nevertheless, to date the exact mechanism of action has not been clarified; it could interact with steroid receptor or may improve the RPE pump, increasing the tissue adenosine levels or blocking the corticosteroid effect

Further investigations are warranted to better understand the role of this treatment modality in the therapeutic approach to chronic forms of CSCR.

Rifampicin

Rifampicin is an antibiotic used for treatment of tuberculosis and leprosy but recently has been reported to have anti-angiogenic [95], anti-oxidative effect and anti-glucocorticoid action [96].

To date, the only prospective study in literature [97] treated 14 eyes with longstanding CSCR with 300 mg of Rifampicin twice a day for 3 months and then 6 months of follow-up. At the end of treatment, mean BCVA improved from 20/60 to 20/50 ($p < 0.05$) and CMT decreased from 476 to 427μm ($p < 0.05$). Four patients showed a complete and stable SRF resolution.

Larger and longer studies are needed to prove Rifampicin efficacy and safety in chronic CSCR treatment.

Melatonin

Melatonin is not only involved in the regulations of circadian rhythm [98] but also has a protective role in ocular diseases, lowering VEGF levels [99], scavenging free radicals [100] and inhibiting glucocorticoid actions [101, 102].

Gramajo et al. [103] treated 13 patients with chronic CSCR with 3 mg of melatonin three times a day for 1 month and 5 patients with placebo. Furthermore, all patients, except one, have already failed to respond to other treatment modalities. In the placebo group, BCVA and CMT remained stable. In contrast, in the melatonin-treated group, BCVA significantly improved ($p < 0.05$) and CMT significantly reduced ($p < 0.01$) at 1 month of follow-up compared to baseline; in particular, 3 patients showed a complete SRF resolution. Only one patient had a CSCR recurrence during the 1 year of follow-up. No adverse effect was observed.

Melatonin seems an affordable alternative treatment for chronic CSCR, but further and larger prospective studies are needed before its use in current practice.

Conclusions

Improvement of choroidal imaging allowed us to better understand CSCR pathophysiology but there is still more to be done.

To date, most widely used treatment in current clinical practice for chronic CSCR are half-fluence/half-dose PDT and SML with large prospective study and on-going clinical

trials should clarify which one and which modalities of them is the most effective and safe.

Promising treatments are MR antagonist and TTT, but further studies are needed to understand their long-term efficacy and safety. In particular, MR antagonist seems effective and relatively safe and requires no expensive equipment compared to SML or PDT. Nevertheless, its success will depend on results of SPECT trial and newer ones. Instead, TTT, routinely used in choroidal lesion treatment, could gain a new therapeutic indication, only if supported by randomized clinical trials, showing efficacy and safety, compared to PDT or SML.

Anti-VEGF treatment is expensive and should be addressed for treating CNV secondary to chronic CSCR.

Finally, oral treatments such as anti-androgenic drugs, MTX, Rifampicin and melatonin, lack large prospective and controlled studies, and actually their role remains at an investigative level.

Nevertheless, in our opinion using a homogeneous definition of the various clinical CSCR forms is critical, like the one suggested by Daruich et al. [1]. In this way, clinical trial could analyse same patterns of patient and compare different treatment modalities to propose safer and more effective therapeutic protocols for different phenotypes. Maybe in future, treatments will be tailored also on the MR haplotypes; in this sense, understanding the pathophysiology of the disease would represent the first step to reach a better and personalized treatment approach.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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