Review Article

Management of chronic central serous chorioretinopathy

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New treatment modalities for the management of central serous chorioretinopathy (CSC) now exist. While acute CSC generally resolves without the requirement for intervention, chronic CSC has been associated with persistent disruption in visual function. Current treatment approaches include photodynamic therapy, oral aldosterone antagonism and subthreshold multifocal laser. There has also been further investigation into a number of new treatments including antivascular endothelial growth factor treatment. Further investigation using developing optical coherence tomography imaging is helping to determine biomarkers of CSC activity, potential indicators of treatment response and indications of chronicity of disease activity. Further comparative study is required to determine the effectiveness of different forms of treatment in a range of patients with varied demographics, aetiology and chronicity of disease.

Key words: Central serous chorioretinopathy, eplerenone, photodynamic therapy, subthreshold laser

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1077_18

Quick Response Code:

Central serous chorioretinopathy (CSC) is a chorioretinal disease characterised by a serous detachment of the neurosensory retina at the macula. It commonly presents with metamorphopsia, central scotoma associated with a modest reduction in visual acuity.[1] Acute CSC often resolves spontaneously within a few months without significant visual impairment.[2] In general, observation with adjustment of modifiable risk factors, particularly cessation of exogenous steroid use and control of systemic hypertension, is a useful initial management option in these cases without requirement for any further intervention.[3]

Recurrent CSC is characterised by multiple spontaneously resolving episodes, whereas patients with chronic CSC appear to have persistent subretinal fluid for at least 3–6 months. Chronic CSC has been suggested to lead to progressive visual dysfunction due to this persistent serous retinal detachment. The pathophysiology of chronic CSC is complex and remains to be fully elucidated. However, it is thought that diffuse retinal pigment epithelium (RPE) decompensation impairs subretinal fluid absorption.[4] Furthermore, indocyanine angiography studies have revealed alteration in choroidal permeability with changes in choroidal vascularity and a thickened choroid, perhaps leading to progressive fluid accumulation.[5]

As chronic CSC has been noted to lead to visual dysfunction, further treatment for CSC is often indicated, after careful discussion with patients. Other factors such as history of previous visual dysfunction due to CSC in the fellow eye and limitations to occupation due to visual symptoms are also important considerations in treatment decisions. Clearly, it is necessary to eliminate modifiable risk factors in these chronic cases also in order to improve response to treatment and optimise visual outcome. A recent Cochrane review evaluating interventions in CSC noted that while intervention in acute CSC may be unnecessary (as it often may be self-limiting), treatment with photodynamic therapy or subthreshold laser could be useful in the treatment of chronic forms.[6] It was noted however that randomised controlled trials comparing treatments to natural history would be useful in identifying treatments that can then evaluated through head-to-head comparison.

The aim of this review was to discuss current treatment strategies in the treatment of chronic CSC. Additionally, new management approaches and further considerations in the general management of chronic CSC are discussed.

Treatment Strategies for Central Serous Chorioretinopathy

Laser photocoagulation

Focal laser photocoagulation has been described as a possible option for the treatment of acute CSC by enabling sealing of any focal RPE defect that causes leakage as demonstrated on fluorescein angiography.[7] Reduction in the neurosensory detachment (NSD) has been reported within 8–10 weeks

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Manuscript received: 26.06.18; Revision accepted: 23.08.18

Cite this article as: Hanumunthadu D, Tan AC, Singh SR, Sahu NK, Chhablani J. Management of chronic central serous chorioretinopathy. Indian J Ophthalmol 2018;66:1704-14.

in studies evaluating acute CSC.[8] Laser photocoagulation, particularly green laser, has been applied with good response in the management of extrafoveal leaks (focal leakage outside of the macula) in acute CSC.[9,10] Other studies, however, have suggested that early focal laser photocoagulation was not better than sham laser, therefore suggesting that observation alone is more appropriate in acute CSC.[11]

Treatment with argon laser photocoagulation, however, has the potential for the development of ocular side effects including development of scotoma or choroidal neovascularization, whereas other studies have suggested that laser photocoagulation treatment may not change the final visual outcome or possibility of recurrence.[12] Laser photocoagulation is currently not accepted generally as a useful treatment in patients with chronic CSC (including in those patients with extrafoveal leaks).

Photodynamic therapy with verteporfin

Treatment of chronic CSC with photodynamic therapy (PDT) and verteporfin was first demonstrated in case series by Chan *et al.* using indocyanine angiography-targeted treatment.[13] It is thought that PDT alters choroidal vasculature structure and perfusion, reducing choroidal permeability.[14] This reduces the subretinal fluid associated with the macular NSD associated with CSC. Many further studies describing treatment of patients with CSC have now been completed [recent studies summarised in Table 1].

Diffuse application of PDT, however, has also been associated with alteration in choroidal pigmentation, RPE atrophy, choriocapillaris nonperfusion and possible choroidal neovascularisation. A rare occurrence of severe choroidal ischaemia has also been reported in patients treated with PDT for CSC.[15] As a result, various studies of modified forms of PDT have been evaluated with modification of PDT fluence, treatment times, dose level and treatment interval.

Half-dose PDT treatment of patients with acute CSC showed complete resolution in 94.9% of subjects compared with 57.9% of subjects treated with placebo only in a prospective randomised study with 12-month follow-up (associated with a statistically significant better best-corrected visual acuity [BCVA] in the PDT-treated group).[16] Hua *et al.* noted that one-third dose of PDT in 68 eyes of 60 patients showed a statistically significant improvement in best corrected visual acuity 6 months after commencement of treatment.[17] It would be useful to determine the minimally required treatment dose PDT to deliver symptom improvement and minimise the possibility of side effects.

In PDT treatment of CSC, hypoxic areas with reduced choriocapillaris flow leads to excess treatment of normal healthy choroidal structure with the possibility of damage to adjacent healthy tissues. Reduction of PDT fluence results in more targeted treatment of affected choroid, limiting RPE disturbance and the possibility of visual dysfunction. Half-fluence PDT was evaluated in a small study of 13 eyes of 11 patients and showed resolution of subretinal fluid in 7 out of 13 eyes after treatment.[18] Reibaldi *et al.* also showed no significant difference in BCVA in 42 subjects with chronic CSC treated with either half-fluence or standard PDT.[19] At 12 months, 8 eyes with standard treatment PDT showed areas of capillary nonperfusion comparing with none of those treated with half-fluence PDT. Furthermore, in a large collaborative retrospective study of 256 eyes of 237 patients treated with PDT, 81% had resolution of subtretinal fluid at last follow-up visit after PDT.[20] Normal fluence was applied in 130 (49%) treatments, half-fluence in 128 (48%) and very low fluence in 7 (3%). No significant difference in treatment outcomes was noted between eye treated and adverse effects were rare. However, increased areas of choriocapillaris nonperfusion were observed in patients with standard PDT. This suggests modification of PDT fluence can still deliver good treatment outcomes with the possibility of reduced side effects. Figs. 1 and 2 show a case of CSC treated with PDT with resolution of subretinal fluid and improved visual acuity. In summary, recent study of modified PDT has suggested that both reduced (most notably half) dose and reduced-fluence PDT can deliver good treatment outcomes in CSC with possible reduced adverse ocular side effects.

Table 1: Overview of recent studies evaluating treatment of patients with central serous chorioretinopathy with photodynamic therapy

Author	Eyes, study design	PDT	Outcome
Doyle *et al.*, 2018[16]	13 eyes, prospective case series	Half fluence	7/13 (resolution of SRF); 4 eyes retreatment; 7/13 improvement 5 ETDRS letters
Lai *et al.*, 2006[60]	20 eyes, case series	Half dose	Mean improvement in BCVA at 1/12 (20/40 to 20/30)
Ruiz-del-tiempo *et al.* 2018[61]	48 eyes, retrospective case series	PDT	Baseline VA was 0.51±0.24 and significantly improved (P<0.001) to 0.74±0.26 one year after PDT
Iacono *et al.*, 2018[62]	19 eyes, prospective case series	Standard PDT	At 1/12 NSD reduced in 12/19 cases with complete resolution in 50% cases
Dhirani *et al.*, 2017[63]	45 eyes, retrospective case series	Half dose, full fluence	BCVA increased at follow up (P<0.05) with rdcution in CRT
Haga *et al.*, 2017[21]	75 eyes retrospective	Half dose	BCVA improved: 0.21±0.24-0.08±0.16
Lai *et al.*, 2016[64]	136 eyes, retrospective case series	Half dose	132 (97.1%) eyes had completed resolution of SRF with 4 (2.9%) recurrence
Breukink *et al.*, 2016[65]	123 retrospective case series	Reduced dose	Complete resolution in 69% of steroid associated cases

PDT: Photodynamic therapy, BCVA: Best-corrected visual acuity, VA: Visual acuity, NSD: Neurosensory detachment, SRF: Subretinal fluid

Table 2: Overview of recent studies evaluating treatment of patients with central serous chorioretinopathy with subthreshold retinal laser

Author	Eyes, study design	Laser parameters	Outcome	Notes
Arsan *et al.*, 2018[66]	39 eyes prospective case series	577 nm SMYL	89.7% improved VA with reduced CMT	
Maruko *et al.*, 2017[67]	15 eyes conventional; 14 eyes subthreshold	NIDEK MC-500 (conventional); IRIDEX IQ577 (subthreshold)	Resolution of SRF 9/14 subthreshold; 10/15 conventional	
Gawęcki *et al.*, 2017[68]	51 eyes, case series	SupraScan 577 Quantel Medical	Resolution of SRF in 70.6%	
Ambiya *et al.*, 2016[69]	10 eyes, prospective case series	Navilas 577 nm		
Breukink *et al.*, 2016[70]	59 eyes, prospective cases series	Iris Medical Oculight SLx 810 nm	At final follow up, 80% had complete resolution of SRF	All eyes received PDT prior to treatment; 10 underwent MPL
Yadav *et al.*, 2015[71]	15 eyes, retrospective case series	SupraScan Quantel Medicel 577 nm	79% average reduction in SRF height	
Abd Elhamid, 2015[72]	15 eyes, prospective case series	IRIDEX IQ577	BCVA improved to 0.67±0.019 6 months after treatment	
Roisman *et al.*, 2013[73]	15 eyes, randomized controlled trial	810nm FastPulse laser	BCVA significantly improved in treatment group (P=0.006)	

PDT: Photodynamic therapy, BCVA: Best-corrected visual acuity, VA: Visual acuity, NSD: Neurosensory detachment, SRF: Subretinal fluid, CMT: Central macular thickness

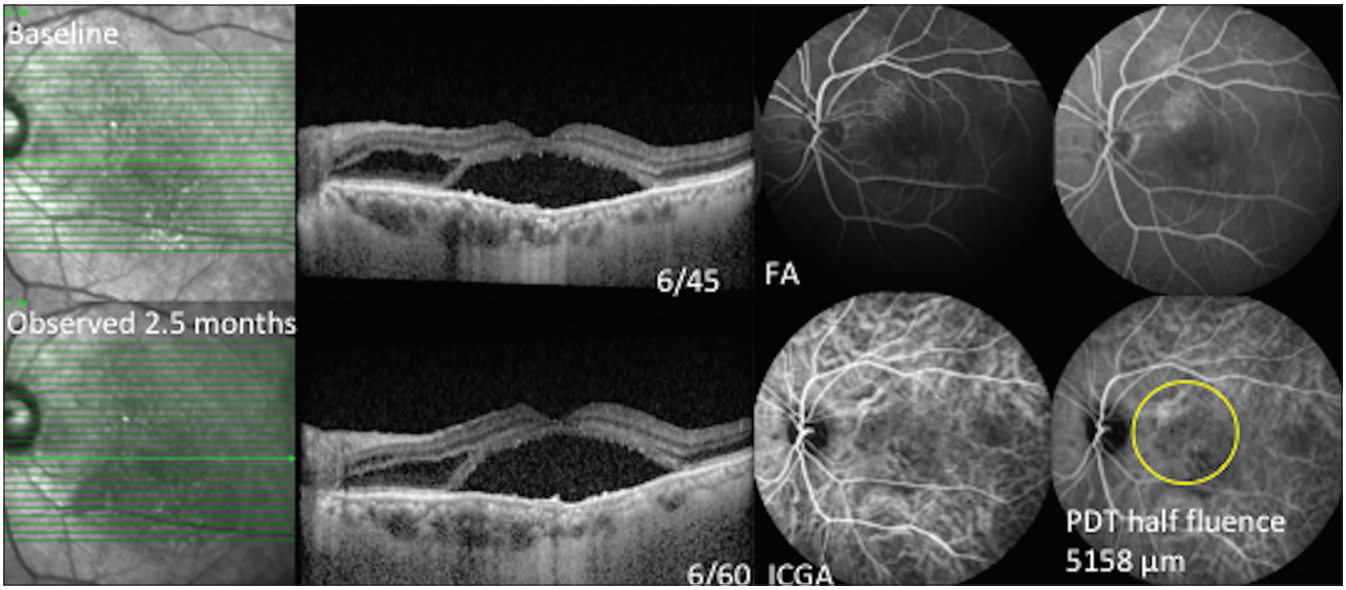

Figure 1: A case of chronic central serous chorioretinopathy (CSCR) treated with photodynamic therapy, Baseline optical coherence tomography (top left), FA (early phase top middle, late phase top right), ICGA (early phase bottom middle, late phase bottom right). The patient was observed for 2.5 months and there was persistence of subretinal fluid (SRD) seen on optical coherence tomography (bottom left) with worsening of vision. Half-fluence photodynamic therapy was then applied to the area demarcated (yellow circle)

PDT treatment of subjects with CSC needs to be evaluated in further studies in particular by further characterisation of its effect on choroidal atrophy and permeability. Long-term outcomes are necessary to study the rates of recurrence and cumulative effects of retreatment. A 3-year follow-up study of 79 eyes of 72 subjects treated with half-dose PDT showed mean improvement in BCVA after 3 years. In those patients unsuccessfully treated with PDT, multivariate analysis suggested that both older age and lower baseline BCVA were associated with poorer visual outcome after treatment.[21] Alteration in subfoveal choroidal thickness (SFCT) has been demonstrated in patients post-treatment with PDT suggesting persistent alteration in choroidal structure after treatment.[22] Indeed, developments in optical coherence tomography (OCT)-guided characterisation of choroidal structure in CSC have revealed alteration in choroidal vasculature in patients with acute and chronic CSC. For example, SFCT and the thickness of Haller's layers appears to be larger both in the affected and uninvolved fellow eye in patients with CSC.[23] Furthermore, OCT angiography has been used to demonstrate alteration in choroidal blood flow in CSC including possible differences between the choriocapillaris and deeper choroidal levels.[24] Detailed phenotyping of these patients using emerging

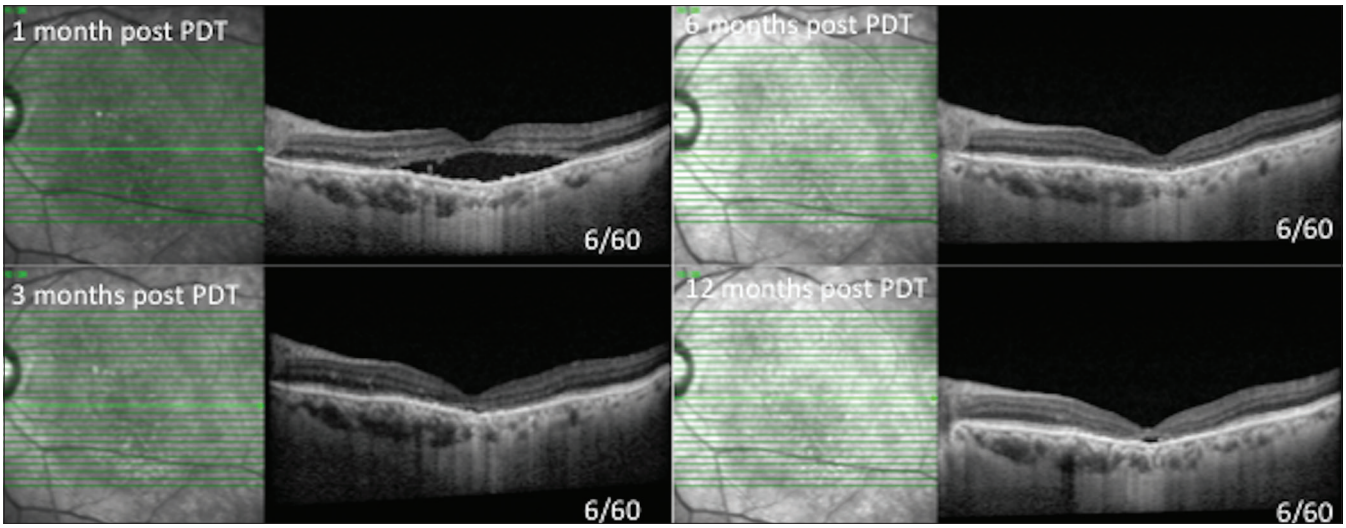

Figure 2: 1-month (top left) post-photodynamic therapy, SRD is less with no improvement in VA; 3-month post-photodynamic therapy (bottom left), there was a resolution of SRD but no visual acuity improvement. A loss of the ISE line is noted on optical coherence tomography that did not resolve with SRD resolution. No visual acuity improvement was noted at 6-month post-photodynamic therapy (top right) or 12-month post-photodynamic therapy (bottom right). A sliver of SRD recurrence was noted at 12-month post-photodynamic therapy

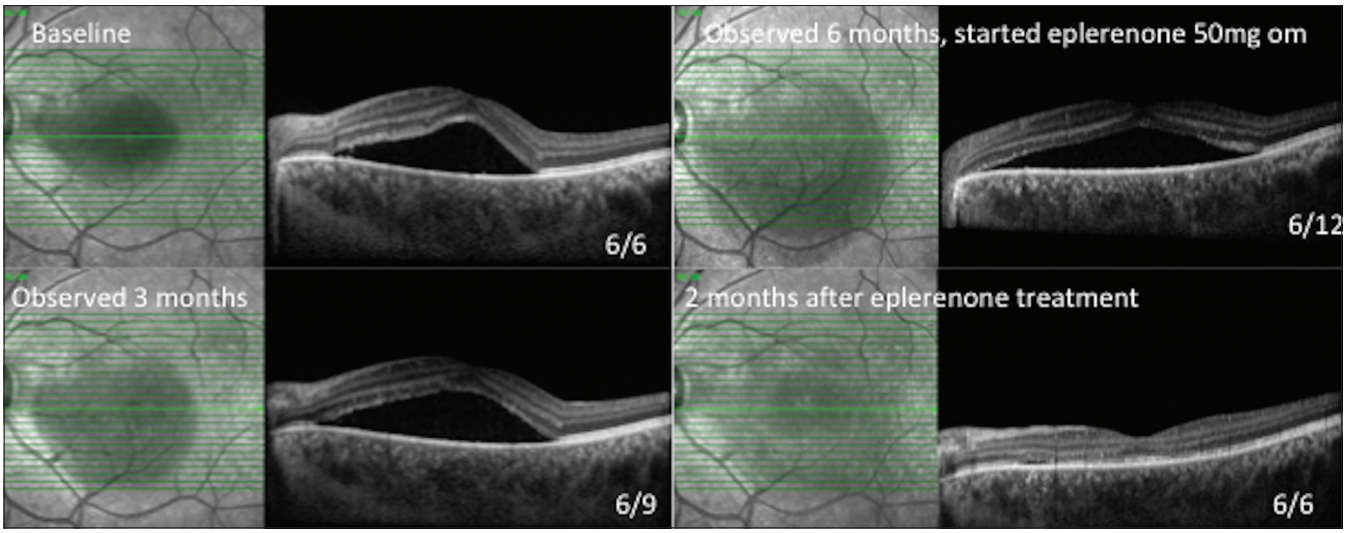

Figure 3: Chronic CSCR seen on optical coherence tomography at baseline (top right) with corresponding VA. Despite observation at 3 months (bottom left) and 6 months (top right), there was worsening SRD and VA. The patient was treated with eplerenone and 2 months after treatment there was complete resolution of SRD and improvement of VA

forms of OCT may be helpful to guide treatment decisions with PDT.

Subthreshold retinal laser treatment

Subthreshold retinal laser therapy has been evaluated in the treatment of various macular disorders. Unlike conventional continuous laser, subthreshold laser minimises associated thermal injury, making it more appropriate for application near to the fovea. It is thought that RPE is almost solely affected without significant treatment on the retina. This may, therefore, prevent the development of central scotoma, retinal scarring and choroidal neovascularisation, all of which have been associated as possible side effects of conventional argon retinal laser treatment. Stimulation of the RPE is thought to be important in repair of the inner blood retinal barrier and regulation of vascular endothelial growth factors (VEGFs) altering RPE permeability. Conventional laser delivers treatment in 0.1–0.5 s, whereas micropulse laser delivers a train of repetitive short laser pulses within the same 0.1–0.5 s.

The 810 nm subthreshold diode laser (near infrared) allows deeper penetration of tissues, in particular the choroid, sparing the inner neurosensory retina and has been evaluated in several studies in the treatment of CSC. The 577 nm laser is a yellow laser that is minimally absorbed by the yellow pigment xanthophyll, thus sparing its action to the inner and outer plexiform layer near the fovea.[25] Published studies of treatment of CSC with subthreshold retinal laser are summarised in Table 2.

Treatment outcomes with subthreshold retinal laser therapy are particularly encouraging, but long-term outcomes, including side effects, require evaluation. Furthermore, standardisation of treatment is needed as these studies have utilised varying laser settings with multiple laser devices. The location of laser treatment, in particular the number and distribution of laser spots applied, varies between trials, whereas there is still controversy over the requirement to apply the treatment at the area of NSD alone, fovea or surrounding normal retina. Previously, it has been suggested that subthreshold laser is more useful in eyes with point-leakage rather that diffuse areas of leakage. This has implications not only for application of treatment but suggests that fluorescein angiography is also mandatory for treatment. Very few studies have reported complications from subthreshold laser. While mild asymptomatic RPE pigmentary changes have been noted, neither development of scars nor choroidal neovascularisation has been reported.[26]

Several of these subthreshold retinal laser studies have varied inclusion criteria and these results may not necessarily be applicable in all patients with chronic CSC. A review of nondamaging retinal laser therapy agreed that there was improvement in both visual acuity and reduced central retinal thickness after treatment but concluded that standardisation of laser settings, careful analysis of indications and more randomised controlled trials are necessary.[27]

Developments in laser technology have allowed more precise targeting treatment. For example, the NAVILAS® laser treatment has been suggested to deliver more targeted laser treatment using eye-tracking technology based on a previously planned fluorescein guided treatment. It was recently reported that treatment with NAVILAS® laser of 32 patients with chronic CSC (duration > 6 months).[28] Complete resolution of subretinal fluid was noted in 17 eyes (50%) after 4 weeks and 24 (75%) after 3 months. No patients were noted to have vision loss due to this treatment. These results need further evaluation in larger studies to determine the efficacy of NAVILAS® laser treatment in CSC.

Mineralocorticoid antagonism

Exogenous steroid use has been consistently demonstrated as a risk factor for development of CSC, while increased expression of ocular mineralocorticoid receptors has been found in eyes of patients with CSC.[3] Activation of steroid receptors can lead to alteration into electrolyte balance affecting generation of subretinal fluid.[29] Spironolactone, an oral aldosterone receptor antagonist, has a high binding affinity for mineralocorticoid receptors. In 18 patients treated in an uncontrolled prospective case series, there was significant reduction in central retinal thickness, NSD and improvement in visual acuity.[30] Spironolactone treatment appeared to show an improvement of 71% cases of nonresolving CSC in a prospective uncontrolled trial with improvement of mean visual acuity from 0.25 to 0.17 logMAR.[31] Hyperkalaemia is a possible side effect of these potassium-sparing diuretics, especially in those with renal disease, suggesting that electrolyte levels requiring monitoring during treatment.

Eplerenone is a mineralocorticoid receptor antagonist used in the treatment of hypertension and congestive heart failure. Eplerenone has been suggested to have increased ocular selectivity with reduced systemic side effects associated with other oral mineralocorticoids (gynaemomastia, erectile dysfunction and menstrual irregularities). Small studies treating patients with chronic CSC with oral eplerenone have shown improvement in visual acuity with reduction of central retinal thickness.[32] Fig. 3 describes a patient with CSC treated with eplerenone with resolution of SRF and improvement in visual acuity. A recent randomised placebo controlled prospective trial consisting of 13 subjects with eplerenone and 6 with placebo concluded that eplerenone was not significantly better than placebo alone.[33] Interestingly, Gergely *et al.* evaluated the use of eplerenone in patients with bilateral chronic CSC that had one eye with exudative CSC and a fellow nonexudative eye.[34] It was shown that in both eyes there was a reduction in choroidal thickness (perhaps due to reduction in choroidal vascularity), although more pronounced in the exudative eyes. Perhaps, mineralocorticoid anatagonism alters choroidal vascular permeability preventing generation of SRF. Indeed animal

Table 3: Overview of studies evaluating treatment of patients with central serous chorioretinopathy with oral mineralocorticoid antagonism (spironolactone or eplerenone)

Author	Eyes, study design	Treatment	Outcome
Herold *et al.*, 2017[31]	21 eyes, interventional prospective uncontrolled trial	Oral spironolactone 50 mg for 16 weeks	71% significant improvement over 12 months
Bousquet *et al.*, 2015[74]	16 eyes, prospective randomised crossover	Oral spironolactone or placebo, washout for 1 week then randomised to placebo or SNL	Reduction in subretinal fluid compared with placebo (P=0.04)
Zucchiatti *et al.*, 2018[75]	15 eyes, retrospective controlled study	Oral eplerenone, versus placebo	At 3 months, BCVA significantly improved (P=0.011) and 12/15 (80%)
Schwartz *et al.*, 2017[33]	Randomised prospective controlled trial, 13 treated, 6 placebo	Eplerenone 50 mg/day or placebo for 3 months then follow up for 3 months	23% reduction in treatment versus 30.8% in control group. BCVA improvement at 3 months better in placebo group (P=0.005)
Rahimy *et al.*, 2018[36]	Prospective randomised controlled trial, 10 treated, 5 placebo	Treatment - eplerenone 25 mg/day for 1 week, then 50 mg for 8 weeks	In treatment group, subretinal fluid height improved (P=0.01) versus control group increased height (P=0.32)
Cakir *et al.*, 2016[76]	24 eyes, retrospective study	Resistant to treatment, 25 mg/day for 1 week, then 50 mg/day	29% complete SRF resolution; 33% transient initial reduction in SRF only

PDT: Photodynamic therapy, BCVA: Best-corrected visual acuity, VA: Visual acuity, NSD: Neurosensory detachment, SRF: Subretinal fluid

studies have described that activation of mineralocorticoid receptors results in choroidal vessel enlargement and permeability, leading to the generation of subretinal fluid.[29,35] Eplerenone treatment may, therefore, enable modification of choroidal physiology without the concurrent risks of treatment with conventional nonmodified PDT regimens.

Table 3 summarises recent studies with both eplerenone and spironolactone for the treatment of CSC. Many of these studies have small numbers with short follow-up time. Furthermore, there have been varying doses of eplerenone used and different treatment lengths in these studies. For example, Schwartz *et al.* evaluated the use of 50 mg dose of eplerenone for 3 months, whereas Rahimy *et al.* evaluated the use of 25 mg/day for 1 week then 25 mg for 8 weeks; both reporting encouraging anatomical and visual outcomes.[33,36] It would be useful to determine the most effective dose regimen and treatment interval needed. Although good observational preliminary studies do exist, further randomized controlled studies with longer follow-up in varying ethnic populations are required to determine the efficacy of treatment. A comparison of the use of eplerenone and spironolactone suggested that while both treatments were effective in delivering absorption of SRF, spironolactone appeared to deliver better BCVA outcomes.[37] However, further head-to-head study between these medicines (at different doses) is needed to fully delineate their role in treatment.

Although well tolerated, treatment with spironolactone and eplerenone requires monitoring of electrolytes (particularly potassium) and liver function. Monitoring intervals may vary according to individual patients, after consideration of pre-existing renal and liver function, although it has been proposed sensible to monitor levels 1 week after commencement of treatment and at monthly intervals.

Anti-vascular endothelial growth factor agents

Various relatively small studies have evaluated the use of anti-VEGF agents in the treatment of CSC. Choroidal hyperpermeability may be associated with increased expression of VEGF and treatment with various anti-VEGF agents has been investigated in CSC. Perhaps unsurprisingly, there have been rather varied outcomes. Indeed, retrospective evaluation of intravitreal bevacizumab treatment in patients with chronic and recurrent CSC (77 eyes of 71 patients) showed reduction in central retinal thickness and associated improved visual acuity.[38] However, a randomised controlled trial of 32 eyes of 34 patients comparing ranibizumab and half-fluence PDT in patients with chronic CSC suggested that PDT treatment was superior (in both resolution of subretinal fluid and improvement in visual acuity).[39]

Anti-VEGF treatment, however, is well established in the treatment of CSC with secondary choroidal neovascular membranes.[40] However, further studies are required to delineate the role of anti-VEGF treatment in CSC generally. It is important to consider the rate of recurrence and need for retreatment after first treatment with anti-VEGF agents. It is possible that previous studies may have also not detected many cases of CSC with secondary choroidal neovascularisation (CNV). In fact, in cases where indocyanine green angiography (ICGA) is not routinely done, secondary CNV can be missed on fluorescein angiography (FA), where diffuse leakage of chronic CSC can mask leakage from a secondary CNV. This, therefore, may be a possible reason why response to anti-VEGF has been variable. Current modalities with optical coherence tomography (OCTA) and OCT show that in the presence of a shallow irregular pigment epithelial detachment (PED) under CSC, atypical to a serous PED, the rate of detection of a secondary CNV is high with both OCTA and ICGA.[41,42]

New forms of OCT technology have improved evaluation of patients with CSC. A recent prospective study (CONTAIN) evaluating intravitreal afibercept shows that treatment was well tolerated after 6 month course and was associated with improved anatomical outcomes but with similar visual acuity outcomes.[43] Furthermore, a recent retrospective study evaluating patients with chronic or recurrent CSC showed that intravitreal bevacizumab was useful in reduced in choroidal thickness and improving visual outcomes at 1 year.[38] These studies have promising results for anti-VEGF treatment in CSC, although it would be useful to also exclude concurrent CNV with OCTA.

Emerging Treatments for CSC

Various new treatment methodologies have been described. Abrishami *et al.* have evaluated the use of low-dose methotrexate as a possible therapeutic option in chronic CSC.[44] They showed complete resolution of subretinal fluid in 13 (63%) of eyes and no

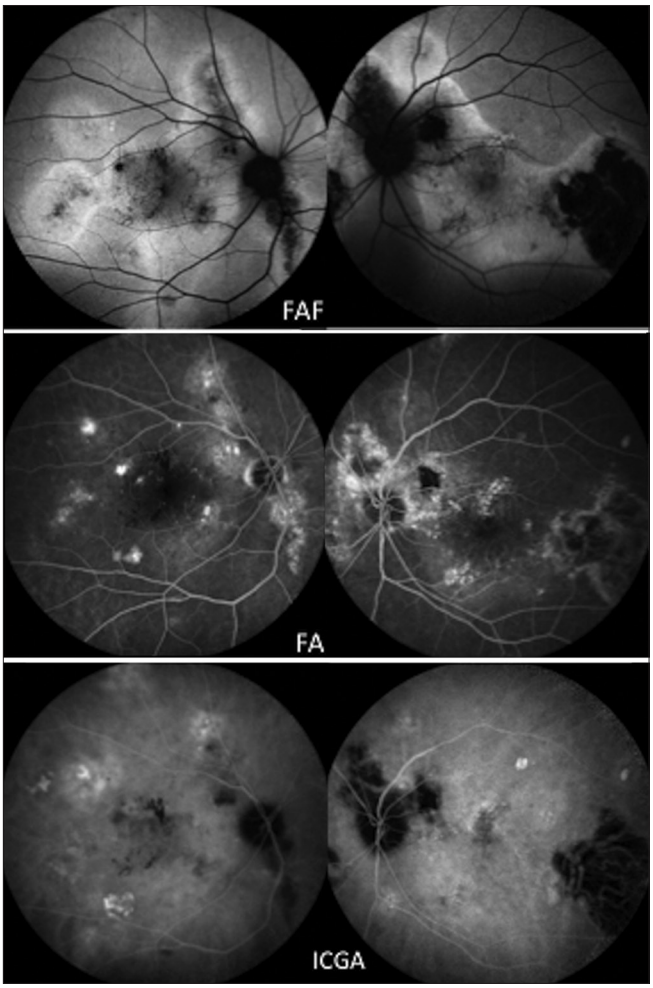

Figure 4: A case of multifocal CSCR seen at baseline with fundus autofluorescence (FAF) (top), FA (middle) and ICGA (bottom)

associated methotrexate toxicity. Treatment with melatonin in a small prospective cases series showed improved visual acuity and reduced retinal thickness.[45] Low-dose salicylic acid was used in the treatment of a relatively large study of 107 patients and demonstrated rapid recovery in visual acuity and low rate of disease recurrence.[46] A multicentre study investigating the effect of lutein supplement on 100 eyes of 100 patients with chronic CSC showed reduced subretinal fluid with significantly improved BCVA.[47] A retrospective review of 29 eyes of 23 patients treated with finasteride reported significant reduction in SRF and improvement in BCVA, although it was also noted a rate of 37.5% recurrence after cessation of treatment.[48]

Considerations in Treatment of CSC

Biomarkers of CSC

Given that acute CSC tends to resolve without the need for intervention, it would be useful to be able to delineate between those patients who were likely to develop chronic CSC at baseline. Chronic CSC has been noted to be associated with atrophic areas of RPE, leakage and patchy staining on fluorescein angiography.[49] Predictive factors including visual acuity and OCT-derived structural parameters may be useful to determine those patients. Lai *et al.* completed a retrospective study of patients with acute CSC that investigated multiple structural parameters important for prognosis.[50] It was concluded that the presence of subretinal and intraretinal hyperreflective dots indicated the need for early intervention. Furthermore, it was suggested that both female and patients agents aged > 50 years also benefited from early treatment. Analysis of patients with CSC has suggested that SFCT at baseline was a useful indicator of chronicity and therefore the requirement for treatment.[51] It would be useful to also determine if earlier treatment is beneficial for these patients. Enhanced-depth imaging OCT has enabled characterisation of choroidal structure and has allowed analysis of choroidal thickness and morphology (particular choroidal vasculature) both at baseline and after various forms of treatment. For example, it has been suggested that SFCT and Haller's layer declined after resolution of treatment in chronic CSC.[23] Future characterisation of OCT parameters may aid to develop treatment outcomes in the clinic and clinical trails of CSC. Treatment decisions may also be affected by the history of previous CSC in the fellow eye including poor visual outcome. Furthermore, anatomical disruption in an affected eye (such as outer retinal disruption and retinal thinning in addition to RPE atrophy) due to CSC may indicate the need for earlier treatment if the fellow eye is affected with CSC.

Analysis of chronic CSC patients with persistent subretinal fluid after PDT treatment revealed that poorer response was characterised by more diffuse leakage on fluorescein angiography, less intense hyperfluoresence on indocyanine angiography, older age and lower BCVA at presentation.[52] In addition to these features, Chung *et al.* noted that other poor prognostic signs for PDT treatment in chronic CSC patients included structural OCT features of shallow irregular pigment epithelial detachment and disruption of the ellipsoid zone.[53] OCT angiography now allows investigation of alteration in choroidal vasculature and flow after treatment. It has already

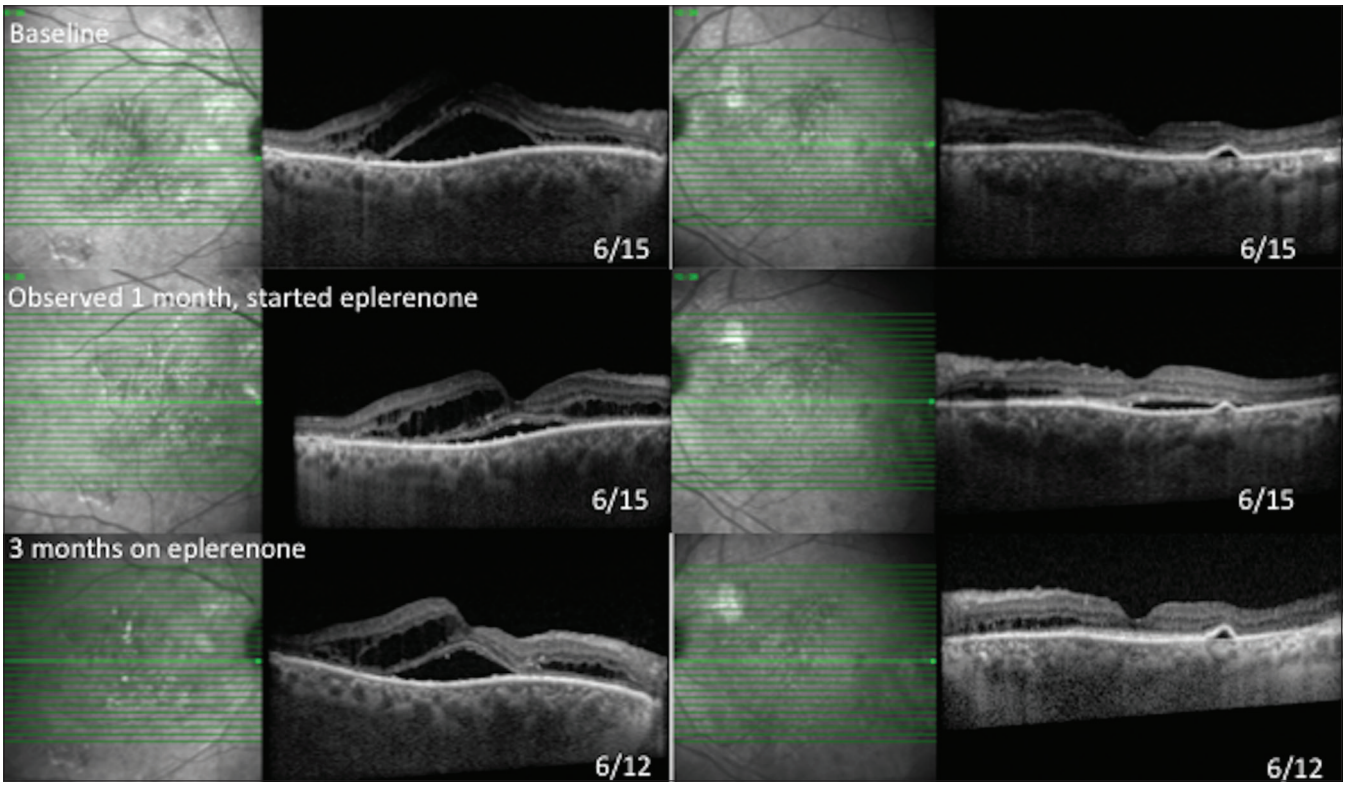

Figure 5: Optical coherence tomography with corresponding VA of the multifocal CSCR seen at baseline (top) with SRD in the right eye and PED and no SRD in the left eye, after 1 month of observation, SRD in the right eye was persistent with increased IR fluid, SRD in the left eye worsened. The patient was treated with eplerenone for 3 months (bottom row) with no resolution of SRD in the right eye and some resolution of SRD in the left eye. VA was improved in both eyes

been reported that choriocapillaris flow appeared to restore itself one month after treatment with half dose PDT.[54] These emerging technologies may enable us to evaluate the therapeutic effects of these treatments on choroidal physiology and develop treatment paradigms depending on OCT angiography biomarkers of choroidal pathophysiology.

Comparative studies

Clearly, various possible treatments with reported efficacy have been described. Indeed, there has been variation amongst practitioners regarding preferred practice in the treatment of CSC suggesting that further work is needed to compare treatment regimens and define treatment strategies to optimise outcomes.[55]

Large prospective randomised controlled trials compared these various treatments head-to-head with extended follow-up time would be useful to determine treatment regimens. A randomised controlled trial comparing PDT and subthreshold laser showed reduced leakage activity on fluorescein angiography and enhanced photopic and scoptopic response from all treated patients compared to placebo.[56] The Pan American Collaborative Retina Study (PACORES) completed a multicentre retrospective comparison of 92 eyes treated with yellow (577nm) laser and 67 with treated with PDT (half-dose verteporfin) and showed similar levels of treatment efficacy between these forms of treatments.[57] It may be useful to determine the benefit of sequential treatment with different modalities. Indeed, it would be useful to determine the effect of multiple treatments. Indeed, it may be the case that certain patients respond better to different forms of treatment and future study should seek to determine the causes of this variation and how they can be determined clinically at baseline. Figs. 4-6 describes a case of multifocal CSR with limited response to eplerenone who then appeared to have anatomical improvement (resolution of subretinal fluid) after treatment with PDT.

Recently, a large multicentre randomised controlled trial showed that half-dose PDT was superior to subthreshold laser (PLACE Trial) with improvement in both resolution of subretinal fluid and functional outcome.[58] 179 patients (89 treated with PDT and 90 with subthreshold laser) were included. At the final visit, PDT-treated patients had significantly better BCVA (P = 0.011). Interestingly, a recent study compared PDT with navigated subthreshold laser in an albeit smaller study (45 eyes of 39 subjects).[59] Navigated laser was applied as confluent spots at areas of focal leakage identified on earliest phase of fluorescein angiography. Navigated laser appeared to be superior to PDT in improving both anatomic and visual function at 6 months. Further study is necessary to see if these results can be repeated with different ethnic populations and ages. It would be useful to know if treatment outcome is dependent upon presence of particular risk factors and treatment response in recurrent treatment.

While exogenous corticosteroid use is well described as a risk factor for the development of CSC, CSC had also been described as an uncommon manifestation of Cushing's

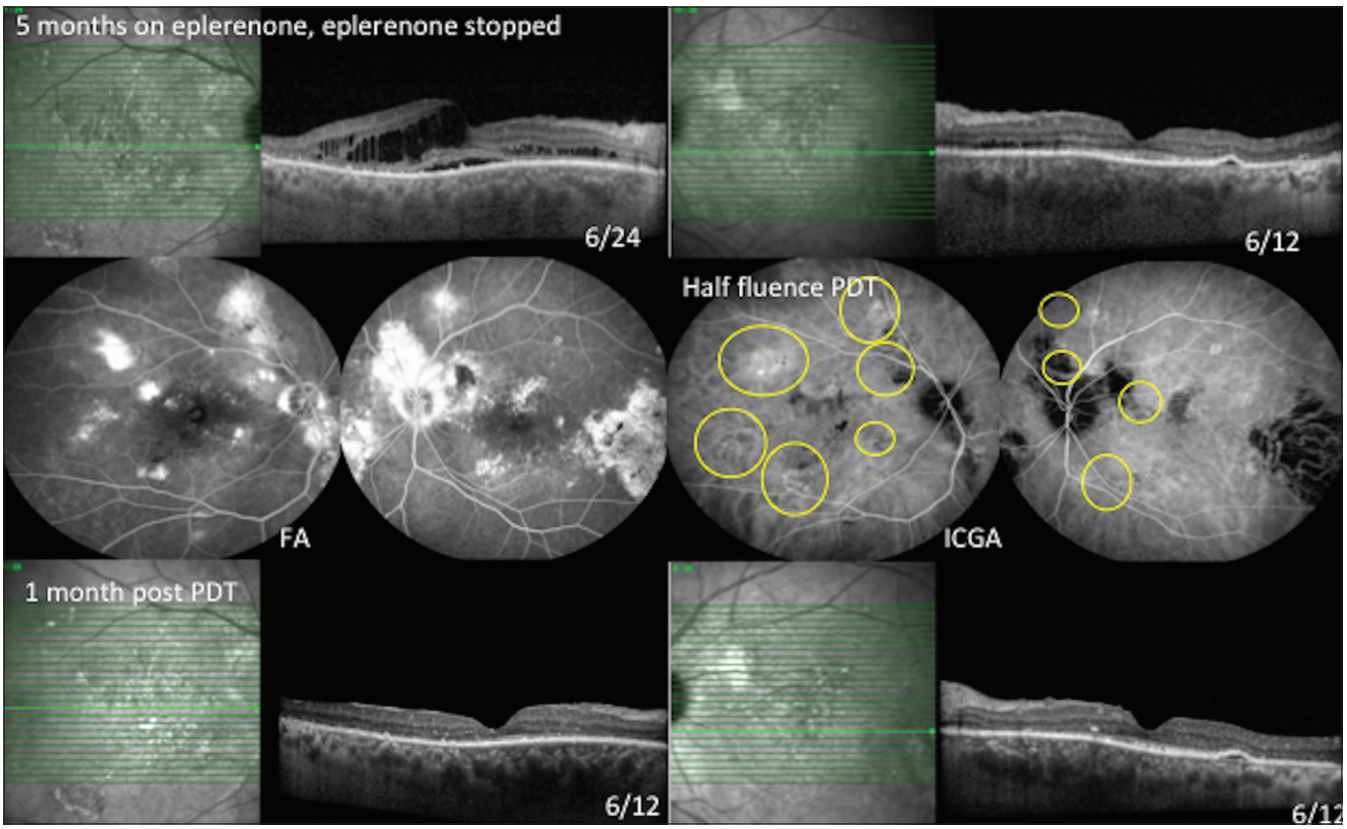

Figure 6: After 5 months of eplerenone (top row), VA worsened with SRD persistence on the right eye. Hence, eplerenone was stopped. FA (middle left) performed showed multiple areas of leakage consistent with multifocal central serous chorioretinopathy (MFCSCR). The patient was treated with ICGA guided half-fluence multispot photodynamic therapy in both eyes (middle right). 1 month after photodynamic therapy, there was an improvement in VA and a resolution of SRD in both eyes (bottom row)

syndrome. It is prudent for an ophthalmologist to inquire regarding common signs and symptoms (including weight gain, development of striae on the abdomen, fatigue, easy-bruising, hypertension, proximal myopathy). In these patients, in consultation with an endocrinologist, it may be necessary to consider further investigation including cortisol and ACTH level, dynamic dexamethasone suppression tests and imaging tests, such as magnetic resonance imaging of the pituitary and adrenal glands.

Conclusion

Several treatment options already exist for the treatment of patients with chronic CSC giving the possibility of improved visual outcome with treatment. Many studies, however, are limited by their retrospective nonrandomised nature with small sample size and limited follow-up. Newer randomised controlled trials have helped to define treatment options for chronic CSC. It is important to recognise that the outcomes of treatment may be affected by particular exogenous risk factors and treatment regimens may need to be refined depending upon these. In the future, analysis of subjects including potential ocular biomarkers of disease activity may help to determine the most appropriate treatment and create individualised treatment regimens.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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