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Central serous chorioretinopathy: Treatment

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Abstract:

Central serous chorioretinopathy (CSC) is a pachychoroid spectrum disease characterized by serous detachment of the neurosensory retina with subretinal fluid in young and middle-aged adults. The pathogenesis of CSC is not yet fully understood. However, it is considered a multifactorial disease that is strongly associated with choroidal dysfunction or vascular engorgement. Although there is no consensus on the treatment of CSC, photodynamic therapy has been effectively used to manage serous retinal detachment (SRD) in CSC. Moreover, micropulse diode laser photocoagulation and focal laser treatment have also been used. Recently, oral medications, including mineralocorticoid receptor antagonists, have been proposed for the management of CSC. Multimodal imaging plays a significant role in the diagnosis and treatment of CSC. Optical coherence tomography angiography (OCTA) has the advantage of detecting vascular flow in the retina and choroid layer, allowing for a better understanding of the pathology, severity, prognosis, and chronicity of CSC. In addition, early detection of choroidal neovascularization in CSC is possible using OCTA. This review article aims to provide a comprehensive and updated understanding of CSC, focusing on treatment.

Keywords:

Central serous chorioretinopathy, micropulse diode laser photocoagulation, mineralocorticoid receptor antagonist, photodynamic therapy

Introduction

Central serous chorioretinopathy (CSC) is the fourth most common chorioretinal disorder worldwide. It has the following characteristics: (1) the condition usually affects young and middle-aged adults, (2) serous retinal detachment (SRD) and/or retinal pigment epithelium (RPE) detachment at the posterior pole with the accumulation of subretinal fluid (SRF), and (3) one or multiple leakage areas that originate from the choroid through an RPE defect on fluorescein angiography (FA).[1-3] In acute cases, FA demonstrates a focal leaking point with an "Inkblot" or "smokestack" dye diffusion pattern. However, multiple leaking points could also be observed.[4] Indocyanine green angiography (ICGA) confirms the delay of initial filling of arteries, dilated large choroidal vein, and choroidal hyperpermeability.[5,6] Previous studies have demonstrated that CSC occurs in the third and fourth decade of life, widely between 20 and 65 years of age.[7-9] Increasing choroidal hyperpermeability and RPE dysfunction contribute to SRF accumulation.[10]

The incidence of CSC has been reported at 9.9 cases/100,000 men compared with 1.7/100,000 women.[7] There are a variety of known risk factors for CSC, such as type A personality, psychosocial stress, corticosteroids, endogenous hypercortisolism, obstructive sleep apnea, *Helicobacter pylori* infection, phosphodiesterase-5 inhibitors (sildenafil, tadalafil), increased cortisol, and pregnancy.[11-19] Corticosteroids are the most common risk factor, and steroid intake in oral, intravenous, skin creams, nasal spray, and joint injection can affect the occurrence, persistence, and recurrence of CSC.[2]

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Further, hypertension and cardiovascular disorders are reported in association with CSC.[20,21]

Acute Central Serous Chorioretinopathy/ Chronic Central Serous Chorioretinopathy

CSC can be classified as acute or chronic forms. However, there is no consensus on the definition and duration for terming chronicity due to the variable course of the CSC and discrepancies with classification among ophthalmologists. Therefore, discrepancies in CSC classification and terminology in clinical studies also cause ambiguity in the diagnosis and treatment of patients with CSC.

Acute CSC generally has a good prognosis. Moreover, acute CSC is usually self-limiting and resolves spontaneously within 3–4 months. In this period, resorption of the SRF is observed in most patients within 3–4 months with the recovery of visual acuity.[22,23] Patients with acute CSC complain of blurry vision, metamorphopsia, and micropsia, but severe vision loss is rare following the condition has resolved. However, recurrent or chronic CSC results in severe visual loss related to atrophy of the RPE and neurosensory layers. Therefore, observation with modification of risk factors is an appropriate treatment for patients with acute CSC.[3]

Chronic CSC is characterized by persistent SRD for longer than 4–6 months, as observed by optical coherence tomography (OCT). In some patients with chronic CSC, permanent atrophy and disruption of the RPE and photoreceptor layer lead to long-term visual impairment, secondary to progressive retinal damage.[24-26] Acute CSC can also lead to multiple recurrences of SRD with persistent SRF. Furthermore, SRF may reappear in 30%–50% of patients within 1 year after the first occurrence of CSC and resolve spontaneously.[27] Although there is no consensus about the definition of chronic CSC, most experts define it as persisting fluid for at least 3–6 months.[28] ICGA–guided verteporfin photodynamic therapy (PDT) has proven to decrease choroidal vascular hyperpermeability and leakage from RPE against chronic CSC. In addition, it has been shown to preserve anatomical function and visual acuity in CSC patients.[29,30]

Pathogenesis

Although the pathogenesis of CSC has not yet been identified, several hypotheses have been proposed to explain it such as the alteration of the outer blood-retinal barrier, the function of the RPE pump due to defective choroidal circulation,[31,32] and mechanical obstructions of the vortex vein.[33,34] Two studies have shown asymmetrical dilatation of the vortex vein in patients with CSC. Furthermore, a recent study demonstrated that patients with CSC had thicker sclera compared with normal eyes, and thicker or rigid sclera showed narrowing of the scleral channel, which results in venous congestion, thus increasing the permeability of the choriocapillaris.[35] The pachyvessels in Haller's layer facilitate mechanical compression of the choriocapillaris and guides the performance of PDT. Moreover, PDT promotes considerable choroidal vessel shrinkage and remodeling, weakening the mechanical compression of the choriocapillaris and improving blood flow.[36]

Although insufficient studies on CSC have been related to systemic inflammatory markers, two studies showed increased levels of inflammatory markers in patients with CSC.[37,38] They suggested that the inflammatory milieu promotes the generation of reactive oxidative species that cause the destruction of RPE and choroid endothelial cells. Similarly, several studies have indicated that activated platelets promote ischemia and thrombogenesis in the choroidal vessels due to choroidal endothelial dysfunction and inflammation, and CSC patients treated with aspirin showed a resolution of CSC with no improved functional outcomes.[38-40]

Corticosteroids are widely accepted as strong factors associated with the development of CSC. Some animal studies have suggested that upregulated choroid endothelial calcium-activated potassium channels cause smooth muscle relaxation, and choroidal permeability results from corticosteroids interacting with mineralocorticoid receptors (MRs).[41] Moreover, corticosteroid dysregulating choroid hemodynamics and interrupting ion transport damage the RPE barrier.[42] Furthermore, cortisol has been demonstrated to downregulate cadherin 5 (CDH5) on choroidal vessels, thereby increasing the choroidal vessel permeability.[43] Likewise, previous research has shown the role of corticosteroids in CSC pathogenesis; however, it remains unclear since many clinical studies associated with MR antagonists have failed to consistently prove its anatomical and functional outcomes. Notably, Lotery A *et al*. showed no benefit of eplerenone in treating chronic CSC.[44] Every patient does not respond equally to MR antagonists, which may be the reason for failing to treat chronic CSC, despite evidence showing its potential role in pathogenesis.[45] Moreover, genetic variants of the MR gene have been proposed as different efficacies or MR antagonists in chronic CSC.[46]

Other risk factors of CSC, such as obstructive sleep apnea, stress, *H. pylori* infection, and increased cortisol are associated with increased oxidative stress that shows reactive oxygen species-mediated damage to choroid vessels and RPE.[14-16] Additionally, CSC is associated with autonomic nervous activity imbalances because the autonomic nervous system regulates the choroid

vessels that cause autonomic dysfunction, leading to vasospasm, which results in choroid ischemia and hyperpermeability.[47,48]

Imaging

FA and ICGA have been used for CSC diagnosis imaging. Imaging technologies such as fundus autofluorescence, OCT and OCT angiography (OCTA) have been developed, and multimodal imaging is currently being used for diagnosing CSC. Since multimodal imaging provides various information on CSC progression or status of the choroid, choriocapillaris, photoreceptor, and RPE, ophthalmologists obtain prognostic information from multimodal imaging when diagnosing, evaluating, and determining the treatment of patients with CSC [Figure 1]. Therefore multimodal imaging techniques allow us to better understand pathology, severity, prognosis, and chronicity.[49]

Treatment

Despite the lack of consensus on the most accepted form of treatment for CSC, observation, oral medications, PDT, and laser therapy have been suggested. For treating CSC, the goal is to resolve SRF, reform vascular permeability, and restore RPE and photoreceptor cells.[50] However, the treatment depends on whether CSC is in the acute or chronic stage. In terms of laser therapy, the conventional laser is applied to extrafoveal focal leak points, micropulse laser to juxtafoveal leaks, PDT to subfoveal leaks, and target choroidal vasculature and RPE cells to increase absorption of SRF or decrease the accumulation of fluid in the subretinal space.[51] Recently, there has been a lot of research about oral medications for treating CSC, compared to laser therapy.

Conventional Laser Photocoagulation

In general, conventional laser photocoagulation involves focal coagulation at the RPE level throughout fluorescein angiography-confirmed areas of the focal leaking point.[52] Nevertheless, conventional laser photocoagulation does not target to the choroid, and the mechanism of SRF resolution following focal laser treatment remains unclear. It is suggested that focal laser injury leads to the recruitment of normal RPE cells or direct stimulation of RPE pumping function around the treatment area.[25,53] Before focal laser treatment, the focal leaking point should be identified at least 375 μm from the fovea.

To reduce the risk of Bruch's membrane rupture, choroidal neovascularization (CNV) development and atrophy of RPE, low intensity, longer duration, and moderate spot size should be used.[25] Studies associated

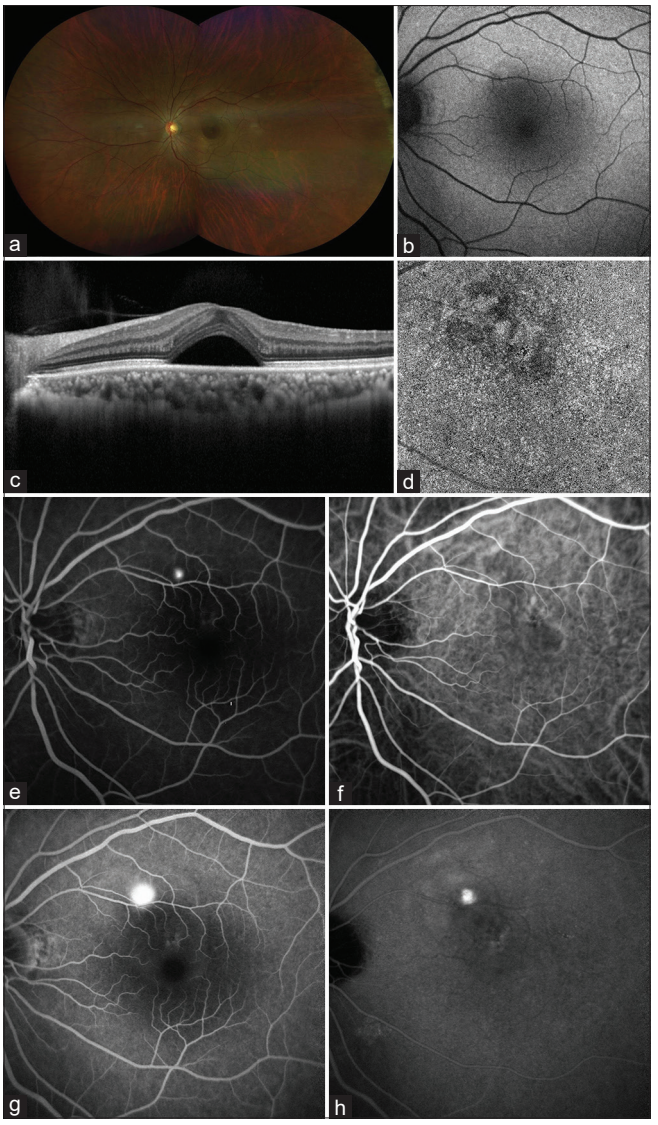

Figure 1: Multimodal imaging of a 46-year-old male patient with CSC. (a) The color fundus photograph shows serous retinal detachment. (b) FAF shows granular hypoautofluorescence in the macula. (c) OCT reveals increased subfoveal choroidal thickness, pachyvessels, and SRF. (d) OCTA of the choriocapillaris layer demonstrates choriocapillary hypoperfusion appearing as a dark spot or dark area related to the SRF. (e) FA shows a focal inkblot leakage pattern in the early phase. (f) ICGA shows dilated choroidal vessels with a focal leakage point in the early phase. (g) FA shows a focal inkblot leakage pattern in the late phase. (h) ICGA demonstrates hyperfluorescence corresponding to the leakage point on FA in the late phase. CSC = Central serous chorioretinopathy, OCTA = Optical coherence tomography angiography, SRF = Subretinal fluid, FA = Fluorescein angiography, ICGA = Indocyanine green angiography, OCT = Optical coherence tomography, FAF = Fundus autofluorescence

with focal laser photocoagulation showed a variety of results regarding BCVA and recurrences.[54-56] Although there is significant anatomical improvement after laser photocoagulation, it is less effective in significantly changing visual acuity and recurrence rate.[25] Burumcek *et al*. reported a decrease in recurrence in the laser photocoagulation group compared with the control group. However, other long-term follow-up studies demonstrated that no significant decrease in recurrence

Table 1: Studies evaluating conventional laser photocoagulation treatment of patients with central serous chorioretinopathy

Author	Study design	Laser	Eyes	Follow-up (months)	Clinical outcomes
Yannuzzi *et al.*[58]	Interventional uncontrolled case series	Krypton red laser	18	18	13% had improved VA. All eyes showed anatomic improvement with partial to complete resolution of the neurosensory detachment at 6 months follow-up
Landers *et al.*[59]	Prospective uncontrolled case series	Argon laser to leak on FA	33	12	85% improved VA, 15% unchanged
Robertson[60]	Prospective randomized single-blinded	Argon laser to leak on FA directly, indirectly, or sham laser	42	18	CSC was reduced by 2 months with direct laser treatment. Direct lasers did not have any recurrence versus 34% of indirect/sham
Gilbert *et al.*[22]	Retrospective case controlled analysis	Argon laser or no treatment	73	58	Treatment had no effect on VA and recurrence rate. 53% of the treated patients resolved within 1 year, and there were no subsequent recurrences

VA=Visual acuity, FA=Fluorescein angiography, CSC=Central serous chorioretinopathy

Table 2: Studies evaluating micropulse diode laser photocoagulation treatment of patients with central serous chorioretinopathy

Author	Study design	CSC type	Laser	Eyes	Follow-up (months)	NSD resolution (%)	Functional outcomes	Anatomic outcomes
van Dijk *et al.*[64]	Open-label multicenter Randomized controlled Clinical trial	cCSC	810 nm micropulse laser Duty cycle: 5% Frequency: 500 Hz Duration: 0.2 s	90	8	29	4.48 ETDRS letter improved at 8 months, mean retinal sensitivity increased +2 dB	
Roca *et al.*[65]	Multicenter retrospective Comparative study	cCSC	Yellow micropulse laser Spot size: 100-200 μm Duty cycle: 5% Power: 320-660 mW	92	12	92	Mean LogMAR BCVA from 0.41 to 0.21	
Koss *et al.*[66]	Comparative controlled Prospective study	CSC	810 nm infrared diode laser Spot size: 125 μm Duration: 200 ms Duty cycle: 15%	52	10	87	Mean BCVA from 16/16 to 2/16	Mean CMT decreased−92 μm
Arsan *et al.*[67]	Prospective study	cCSC	577 nm supra 577 Y subliminal laser Spot diameter: 160 μm Duration: 20 ms Duty cycle: 5%	39	12	92	Mean BCVA increased +0.43 (snellen), mean contrast sensitivity improved +0.49 dB	Mean CMT decreased−119 μm
Arora *et al.*[68]	Randomized controlled trial	aCSC	810 nm infrared diode laser Spot size: 125 μm Pulse envelopes: 100×300 μs micropulses Duty cycle: 15%	34	6	N/A	Mean LogMAR BCVA improved−0.56, mean contrast testing chart improved +0.51	Mean SRF height decreased−239 μm, CMT decreased−99 μm
Scholz *et al.*[69]	Retrospective study	cCSC	577 nm micropulse laser Spot size: 160 μm Duty cycle: 5% Duration: 0.2 s	38	5	24	Mean LogMAR BCVA improvement: 0.06	Mean CRT decreased−115 μm
Gawęcki *et al.*[70]	Retrospective study	cCSC	577 nm yellow micropulse Spot size: 160 μm Power: 250 mW Exposure: 0.2 s Duty cycle: 5%	51	12	71	Mean LogMAR BCVA improved−0.08	Mean foveal CRT decreased−130 μm

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was found between the laser-treated group and the control group.[23,25,56,57] Adverse events following laser photocoagulation treatment, such as CNV, are typically low. Moreover, it should be considered that paracentral scotoma may develop following laser treatment in the juxtafoveal area.[23,25] The studies evaluating conventional laser photocoagulation treatment of patients with CSC are summarized in [Table 1].

Table 3: Studies evaluating photodynamic therapy of patients with central serous chorioretinopathy

Author	Study design	CSC type	Laser	Eyes	Follow-up (months)	NSD resolution	Functional outcomes	Anatomic outcomes
Yannuzzi *et al*.[90]	Prospective noncomparative case series	cCSC	Standard	20	Mean of 7 months	60%	In 6 eyes, VA improved by more than 2 lines and remained stable in 14 eyes	2-6 weeks after treatment, all eyes had complete resolution ICG hyperpermeability at the site of treatment
Cardillo Piccolino *et al*.[29]	Noncomparative case series	cCSC	Standard	16	6-12	81%	VA improved from 1 to 4 lines in 11 eyes (69%) and was unchanged in 5 eyes (31%) after 3 months	In 2 eyes, retinal thickness decreased with cystoid macular changes
Iacono *et al*.[91]	Prospective case series	cCSC	Standard	19	12	95%	Mean BCVA improved by 14.4 letters (P=0.001) at 12 months	
van Dijk *et al*.[64]	Prospective double-blind randomized controlled trial	cCSC	Half-dose	89	7-8	67%	Mean ETDRS letters improved +7, mean retinal sensitivity improved +3 dB Post-PDT BCVA was correlated with baseline BCVA (r=0.70, P<0.001)	
Lim *et al*.[92]	Retrospective case series	cCSC	Standard or reduced setting	237	1-12	81%	Post-PDT BCVA was correlated with baseline BCVA (r=0.70, P<0.001)	
Fujita *et al*.[93]	Retrospective interventional case series	cCSC	Half-dose	204	12	89%	Mean LogMAR BCVA from 0.11 to 0.01 at 12 months (P<0.0001)	Persistent SRD of 11 eyes and recurrence of 12 eyes after earlier resolution were observed during the follow-up period
Sheptulin *et al*.[94]	Retrospective case series study	cCSC	Half-time	114	12	87%	Median improvement of LogMAR BCVA from 0.22 to 0.1 (P<0.0001)	
Zhao *et al*.[83]	Double-masked randomized controlled clinical trial	aCSC	Half-dose or 30% dose	131	12	75% (30% dose group) 95% (half-dose group)	Mean ETDRS letters from 75 to 83 in the 30% dose group and from 75 to 85 in the half-dose group	
Ozkaya *et al*.[95]	Retrospective case-control study	cCSC	Half-fluence	101	3	N/A	Regarding OCT and FA findings there was no significant difference between responders and nonresponders to PDT, for all the evaluated findings (P>0.05 for all)	
Ruiz-Moreno *et al*.[77]	Nonrandomized, multicenter, interventional case series	cCSC	Standard	82	Mean of 12 months	100%	Mean LogMAR BCVA from 0.53 to 0.37	
Oh and Yu[86]	Retrospective, comparative interventional case series	cCSC	Full-fluence or half-fluence	Full-fluence: 25 Half-fluence: 43	Mean of 16 months	N/A		SFCT decreased from 351 μm (full-fluence) and 362 μm (half-fluence)-267 μm and 318 μm at 12 months respectively
Alkin *et al*.[96]	Retrospective comparative	cCSC	Low-fluence or half-dose	Low fluence: 36	12.5±4.3 in low-fluence	92% (low-fluence	Mean BCVA increased by 7	In both groups, significant decreases

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Table 3: Contd...

Author	Study design	CSC type	Laser	Eyes	Follow-up (months)	NSD resolution	Functional outcomes	Anatomic outcomes
	study			Half-dose: 28	group, 13.1±4 months in half-dose group	group) 93% (half-dose group)	ETDRS letters in the low-fluence group, and by 5 ETDRS letters in the half-dose group	in the central foveal thickness were observed
Shin *et al*.[97]	Retrospective comparative study	cCSC	Full-fluence versus half-fluence	60	Mean of 13 months	94% (half-fluence) 100% (full-fluence)	No difference in final LogMAR BCVA between the 2 groups (0.17 versus 0.21; *P*=0.603)	
Nicoló *et al*.[98]	Retrospective comparative case study	cCSC	Half-fluence versus half-dose	Half-fluence: 31 Half-dose: 29	12	84% (half-fluence group) 100% (half-dose group)	Mean logMAR BCVA improved significantly at 12 months from 0.187 to 0.083 in the half-fluence group and from 0.126 to 0.68 in the half-dose group without a significant difference between the 2 groups	9 eyes (29%) in the half-fluence group and 5 eyes (17.2%) in the half-dose group had recurrence of SRF during follow-up
Lai *et al*.[99]	Retrospective multicenter interventional case series	cCSC	Half-dose	136	Mean of 58 months	97% (36 months after treatment)	Mean LogMAR BCVA from 0.36 to 0.15 at 36 months, 32.4% had improved BCVA by 3 lines and 3.7% had reduced BCVA by 3 lines at 36 months	9 eyes (6.6%) had recurrence, 5 eyes retreated and 4 eyes resolved spontaneously
Liu *et al*.[100]	Retrospective comparative case series	aCSC or cCSC	Half-dose or half-time	Half-dose: 35 Half-time: 26	Mean of 15 months	91% in the half-dose group versus 100% in the half-time group	Half-dose group from 0.39±0.2 logMAR at baseline to 0.25±0.19 logMAR at 12 months, half-time from 0.29±0.20 logMAR at baseline to 0.15±0.09 logMAR at 12 months	3 eyes in the half-dose group and 2 eyes in the half-time group had recurrence during follow-up
Kim *et al*.[101]	Retrospective comparative case series	cCSC	Half-fluence or half-dose	Half-dose: 26 Half-fluence: 26	Mean of 21 months in the half-fluence group and 22 months in the half-dose group	96%	In half-fluence group, mean BCVA significantly changed from 0.31 to 0.11 and half-dose group, mean BCVA changed from 0.31 to 0.12, no significant difference between the groups	Complete photoreceptor recovery was found in 19 and 14 eyes in the half-fluence and half-dose groups respectively (*P*=0.150), no significant difference in any parameters between the groups
Tseng and Chen[102]	Retrospective interventional case series	cCSC	Half-dose	56	Mean of 56 months	100% (at 12 months)	Mean LogMAR BCVA significantly changed from 0.36 to 0.13 at 6 months and remained stable there after	4 eyes developed recurrence after one session of PDT
Son *et al*.[31]	Retrospective study	cCSC	Full-fluence or half-fluence	Full-fluence: 37 Half-fluence: 30	36	100%	Mean LogMAR BCVA improved significantly in both the full-fluence group (from 0.34 to 0.15)	CMT improved significantly in both the full-fluence and half-fluence groups at 36 months, without a

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Table 3: Contd...

Author	Study design	CSC type	Laser	Eyes	Follow-up (months)	NSD resolution	Functional outcomes	Anatomic outcomes
							and half-fluence groups (from 0.36 to 0.15) at 36 months, without a significant difference between the groups	significant difference between the groups. Both groups showed significant reductions in SFCT with full-fluence (416.8-316.8 μm) being better overall than half-fluence (409.7-349.1 μm, *P*=0.002)
Noh *et al*.[32]	Retrospective study	cCSC	Focal spot size or conventional spot size	Focal: 26 Conventional: 26	12	100%		Mean baseline SFCT for the 2 groups was 334.95 and 348.35 μm, respectively, with no significant difference. SFCT decreased significantly to 265.95 μm at 12 months in the focal group, and in the conventional group, decreased significantly to 272 μm at 12 months. No significant differences between the 2 groups in SFCT based on PDT spot size at 1, 3, 6 and 12 months

CSC=Central serous chorioretinopathy, aCSC=Acute CSC, cCSC=Chronic CSC, NSD=Neurosensory detachment, VA=Visual acuity, BCVA=Best-corrected VA, ETDRS=Early treatment diabetic retinopathy study, CMT=Central macular thickness, SFCT=Subfoveal choroidal thickness, PDT=Photodynamic therapy, LogMAR=Logarithm of the minimal angle of resolution, FA=Fluorescein angiography, ICG=Indocyanine green, OCT=Optical coherence tomography, SRD=Serous retinal detachment, N/A=Not available, SRF=Subretinal fluid

Micropulse Diode Laser Photocoagulation

Unlike conventional laser photocoagulation, micropulse diode laser therapy delivers a series of ultrashort (810 nm) laser pulses targeting RPE cells with little thermal damage to the RPE and collateral tissues because of the relatively small amounts of energy.[61,62] It is considered that only the RPE is affected without significantly affecting the retina. Thus it prevents paracentral scotoma, retina scarring, and CNV compared with conventional laser photocoagulation. Micropulse diode laser photocoagulation is useful in patients with chronic CSC with juxtafoveal leaking points or diffuse epitheliopathy. However, it is difficult to assess laser uptake because micropulse diode laser photocoagulation does not cause visible laser burns. To resolve invisible laser burns, Ricci *et al*. reported an indocyanine green-assisted micropulse diode laser.[63]

One randomized controlled trial demonstrated no statistical difference between the micropulse diode laser photocoagulation and argon laser groups in terms of SRF resolution and final BCVA. However, the micropulse diode laser photocoagulation group showed significantly better contrast sensitivity than the argon laser group. Additionally, no persistent scotoma was found in the micropulse diode laser photocoagulation group, but 20% of the argon laser group patients showed scotoma.[62] The studies evaluating micropulse diode laser photocoagulation treatment of patients with CSC are summarized in [Table 2].

Photodynamic Therapy

PDT with verteporfin provides high efficacy for SRF resolution, improvement of VA, and reduced recurrence of SRF in patients with chronic CSC. Verteporfin is a photosensitizing agent that is a mixture of benzoporphyrin-derivative monoacids that are cytotoxic only when activated by light in the presence of oxygen. It stimulates the macula at a specific light dose. In PDT treatment, free radicals are released when verteporfin molecules are excited by lasers. Free radicals result in inflammation of the choroidal vascular wall and cause occlusion of the choroidal vessels.[71] Therefore, PDT is suggested to cause a decrease in choroidal hyperpermeability by short-term choriocapillaris hypoperfusion and long-term choroidal microvascular

Table 4: Studies evaluating anti-vascular endothelial growth factor treatment of patients with central serous chorioretinopathy

Author	Study design	CSC type	Interventions	Eyes	Follow-up (months)	NSD resolution	Functional outcomes	Anatomical outcomes
Kim *et al*.[108]	Prospective randomized comparative study	aCSC	Single dose of ranibizumab (0.5 mg)	20	>6	100%	Mean LogMAR BCVA from 0.37 to 0.17	
Tekin *et al*.[113]	Retrospective comparative study	aCSC	Either bevacizumab (1.25 mg) or ranibizumab (0.5 mg)	43	Mean of 18 months	100% (near complete resolution)		Mean CMT decreased 3 µm
Bae *et al*.[111]	Prospective noncomparative	cCSC	3 consecutive monthly injections of 0.5 mg ranibizumab	16	12	13%	Mean BCVA improved 0.19 LogMAR	Mean CMT decreased 71 µm
Lim and Kim[114]	Prospective, noncomparative	CSC>3 months	1 or 2 intravitreal injection (s) of 1.25 mg bevacizumab if SRF present at 6 weeks	40	>12	83% (within 3 months)	Improved group: Mean LogMAR BCVA from 0.25 to 0.09 Persistent group: Mean LogMAR BCVA from 0.25 to 0.2	Improved group: CMT reduction from 432 µm to 201 µm Persistent group: CMT reduction from 432 µm to 377 µm
Kim *et al*.[115]	Retrospective study	Persistent CSC	Intravitreal injection (s) of 1.25 mg bevacizumab, as needed	42	Mean of 9 months	60%	Mean LogMAR BCVA from 0.35 to 0.32	Mean CMT decreased 60 µm
Peiretti *et al*.[116]	Retrospective study of a consecutive series	CSC with neovascularisation	Either bevacizumab (1.25 mg) or ranibizumab (0.5 mg) or pegaptanib (0.3 mg)	18	12	N/A	Mean LogMAR BCVA from 0.69 to 0.39	
Roy *et al*.[117]	Retrospective case series	CSC with choroidal neovascular membrane	Either bevacizumab (1.25 mg) or ranibizumab (0.5 mg)	10	Mean of 28 months	60%	Mean LogMAR BCVA from 0.62 to 0.47	
Ünlü *et al*.[118]	Retrospective comparative study	Unspecified	Intravitreal injection (s) of 1.25 mg bevacizumab, as needed	22	Mean of 12 months	100% (near complete resolution)	Mean LogMAR BCVA from 0.38 to 0.24	Mean CMT decreased 135 µm
Kim *et al*.[119]	Retrospective noncomparative	Unspecified	Multiple intravitreal injection (s) of 1.25 mg bevacizumab	30	>6	67%		SFCT (nonresponders group) increased 3 µm, SFCT (responders group) decreased 63 µm
Pitcher *et al*.[112]	Prospective noncomparative	cCSC	1 intravitreal injection of 2.0 mg aflibercept	12	6	50%	Mean ETDRS letters from 62 to 64	

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remodeling, resulting in SRF reabsorption.[72,73] Some authors have suggested that direct effect by PDT on the choriocapillaris endothelium with the choriocapillaris occlusion, resulting in stasis of blood flow and reduction in vascular permeability.[74] In addition, choroidal thickness decreases within 1 month after PDT treatment. Following PDT, choroidal thickness is reduced, both locally and at a considerable distance from the treated area, altering intrachoroidal structures. Thus, the process that causes choroidal thickening in CSC appears to spread laterally within the choroid.[75,76] Moreover, the photoreceptor layer is usually not damaged because of the high selectivity of PDT.[72] PDT is possible even in cases of chronic CSC with juxtafoveal or subfoveal leakage points or diffuse RPE leakage. Therefore, PDT is considered a more appropriate treatment for CSC pathology.

Generally, standard PDT is given with a 6 mg/m² verteporfin dose, 50 J/cm² fluence, 83 s of time, and a spot size larger than 1000 µm to be treated, guided by ICGA. Verteporfin was diluted in 30 ml of infusion solution and administered via IV infusion over 10 min. Light activation by PDT was performed 15 min after

Table 5: Studies evaluating mineralocorticoid receptor antagonist of patients with central serous chorioretinopathy

Author	Study design	CSC type	Drug/dosage/ duration	Eyes	Follow-up (months)	NSD resolution	Functional outcomes	Anatomical outcomes
Sun *et al*.[134]	Prospective randomized controlled clinical study	aCSC	Spironolactone 40 mg, twice daily for 2 months	30	2	56%	Mean LogMAR BCVA from 0.25 to 0.05	Mean CMT decreased from 536 to 248 μm
Kim *et al*.[138]	Retrospective interventional comparative study	Nonresolving CSC	Spironolactone 50 mg daily	26	Mean of 15.2 months	69%	Mean LogMAR BCVA from 0.39 to 0.2	
Schwartz *et al*.[128]	Prospective double-blind randomized placebo-controlled study	cCSC	Eplerenone 25 mg for 1 week, 50 mg after 1 week	13	Up to 6 months after the start of treatment	23% (after 3 months)	Mean LogMAR BCVA from 0.50 to 0.48 (not significant)	
Sacconi *et al*.[139]	Interventional open-label nonrandomized clinical study	cCSC	Eplerenone 25 mg for 1 week, 50 mg after 1 week, maximum 13 weeks	29	21 weeks	58%	Mean LogMAR BCVA from 0.20 to 0.10 at the end of treatment	Mean SFCT decreased 21 μm
Daruich *et al*.[140]	Retrospective case series of consecutive patients	Nonresolving CSC	Eplerenone versus spironolactone 25 mg for 1 week, 50 mg after 1 week	54	6 months after treatment	50%	0.05 LogMAR gain at 6 months	Mean CMT decreased 57 μm
Pichi *et al*.[130]	Prospective placebo-controlled trial	Persistent CSC	Eplerenone versus spironolactone 25 mg for 1 week, then increase to 50 mg, with crossovers	60	4	N/A	Significant improvement in treatments arms compared to placebo	Both spironolactone and eplerenone did not show a statistical reduction in choroidal thickness (17 and 15 μm mean reduction,respectively)
Lotery *et al*.[44]	Randomized double-blind placebo-controlled study	cCSC	Eplerenone (25 mg/day for 1 week, increasing to 50 mg/day for up to 12 months) or placebo up to 12 months	114	12	16%	No significant benefit of eplerenone with regards to distance visual acuity. Eplerenone was not superior to placebo for improving BCVA in people with cCSC after 12 months of treatment	
van Rijssen *et al*.[129]	Multicenter open-label randomized controlled trial	cCSC	Eplerenone 25-50 mg/day or 25 mg every 2 days	107	3	17%	Mean ETDRS letters from 80.4±7.9 to 82.8±9.0	Mean central retinal thickness at baseline was 104.0±19.0 μm to 113.4±24.8

CSC=Central serous chorioretinopathy, aCSC=Acute CSC, cCSC=Chronic CSC, NSD=Neurosensory detachment, BCVA=Best-corrected visual acuity, ETDRS=Early treatment diabetic retinopathy study, CMT=Central macular thickness, SFCT=Subfoveal choroidal thickness, LogMAR=Logarithm of the minimal angle of resolution, N/A=Not available

the start of infusion. PDT can be applied to single or multiple areas; if SRF persists after PDT treatment, retreatment should be performed at least 3 months later because reducing the treatment interval has no benefit.

However, several studies have reported on dose-dependent complications. Ruiz-Moreno *et al*. reported that 82 eyes with chronic CSC were treated with a standard PDT protocol, and all eyes showed resolution of SRF. Despite this, two eyes developed iatrogenic CNV, nine developed RPE hyperplasia, and repeated PDT was required in thirteen patients.[77] Standard PDT's complications and risks, including iatrogenic CNV, pigmentary changes in the treated area, foveal injury, and RPE atrophy, pose a threat to visual outcomes.[78,79] Therefore, to address the safety concerns and reduce the adverse events related to standard PDT, investigators considered changing the PDT setting parameters such as lowering the fluence or PDT dose, and laser treatment time to decrease the risk of complications while maintaining treatment efficacy.[73,80] Low-dose PDT, which uses half dose of verteporfin (3 mg/m^2) and low-fluence PDT, has proven to be an effective treatment for the resolution of chronic CSC.[74,81-84] A prospective nonrandomized clinical trial compared the efficacy and safety between half-fluence and full-fluence PDT.[84] At 12 months, BCVA improvement was observed in both

groups; however, there was no difference between them. Moreover, SRF reabsorption was found in 79% and 91% of the full-fluence and half-fluence groups, respectively. The other prospective, nonrandomized clinical trial compared the efficacy and safety between half-fluence and half-dose PDT for 6 months.[85] The results revealed no significant differences in the parameters between the two groups. Therefore, half-dose and half-fluence PDT had similar therapeutic effects in improving visual acuity and SRF absorption in chronic CSC.

One retrospective study reported improvement in BCVA and central retinal thickness; however, the differences between groups were not statistically significant.[86] Moreover, subfoveal choroidal thickness decreased in both groups; the full-fluence group showed a greater reduction of subfoveal choroidal thickness than the half-fluence group. Another retrospective study compared the clinical outcomes of 192 CSC patients divided into untreated and half-dose PDT groups (treatemt group) with a minimum follow-up of all patients was 36 months.[87] In the half-dose PDT group, BCVA was significantly better while recurrence of CSC was significantly lower, at the last follow-up. Furthermore, the other prospective, noncomparative case series studies assessing half-dose PDT showed visual improvements and complete SRF absorption.[88,89]

According to the long term clinical outcomes of a retrospective study evaluating full-fluence and half-fluence PDT for 36 months, either a full-fluence or half-fluence protocol was effective with significant long-term improvement in anatomic and functional outcomes with no recurrences, and very few cases of RPE atrophy were observed with both protocols.[31] Furthermore, to decrease the risk of complications, a study was conducted on PDT spot size.[32] Noh *et al*. reported that focal verteporfin PDT, confined to areas of localized leakage demonstrated in ICGA compared with conventional verteporfin PDT, covered the total area of abnormal choroidal vessels, including the leakage, resulting in a significant decrease in SRF and subfoveal choroidal thickness as well as conventional PDT during the 1-year follow-up.[32] RPE atrophy was observed as a complication in one eye and three eyes in the focal and conventional verteporfin PDT groups, respectively. However, there was no statistical difference between the two groups.

Recently, a study on the efficacy of treatment with high-density subthreshold micropulse laser (HSML) and PDT in patients with chronic CSC has been conducted.[64] The PLACE trial is the largest multicenter, randomized controlled clinical trial to compare the anatomic and functional efficacy and safety of half-dose PDT versus HSML treatment in patients with chronic CSC. At the final evaluation visit, a significantly higher percentage of PDT-treated patients demonstrated no SRF (67.2% vs. 28.8%; $P < 0.001$). Moreover, the PDT-treated patients showed a significantly higher increase in BCVA and a significantly higher increase in retinal sensitivity. Therefore, half-dose PDT is superior to HSML for treating chronic CSC, leading to a significantly higher proportion of patients with complete resolution of SRF and functional improvement.[64]

There are few randomized studies evaluating PDT in CSC patients despite its many therapeutic advantages, and further investigation is needed to standardize PDT treatment in terms of dose, fluency, and time. The studies evaluating PDT treatment of patients with CSC are summarized in [Table 3].

Anti-Vascular Endothelial Growth Factor Therapy

Intravitreal anti-vascular endothelial growth factor (VEGF) injections have been suggested to effectively reduce choroidal hyperpermeability and proliferative activity of choroidal endothelial cells without clear evidence of increased VEGF levels in the aqueous humor of patients with CSC.[103,104] Additionally, anti-VEGF is thought to control the tight junctions between endothelial cells and reduce vascular fenestrations.[105]

Altering choroidal vascular permeability with intravitreal anti-VEGF injection has been suggested as a possible treatment for CSC since CSC is thought to be related to choroidal vasculature.[106] However, anti-VEGF therapy for treating CSC is generally off-label. The effects of anti-VEGF treatment in patients with CSC have been reported in various ways.

Several studies have proven the efficacy of anti-VEGF therapy associated with the resolution of neurosensory detachment and improvement of visual acuity.[107,108] Moreover, the anti-VEGF agent may be a better treatment compared with PDT in CSC patients with fibrin observed in the fovea, indicating abnormal choroidal vessel leakage.[109] In cases where verteporfin molecules bind to fibrin and PDT may cause RPE damage with energy accumulation, anti-VEGF therapy prevents complications.

However, the positive therapeutic effects of intravitreal anti-VEGF injections for CSC have not been confirmed in a meta-analysis. Bae *et al*. performed a prospective, randomized study of chronic CSC comparing ranibizumab with half-fluence PDT.[110,111] This study demonstrated the superiority of PDT over ranibizumab in terms of complete resolution of SRF and decreased

choroidal hyperpermeability. Furthermore, chronic CSC patients treated with aflibercept appeared to have a significant resolution of SRF but no significant improvement in visual acuity in the contain study that suggested aflibercept showed clinical efficacy for better anatomical outcomes rather than functional outcomes.[112]

Although many studies have been conducted on anti-VEGF therapy for patients with CSC, no large randomized controlled clinical trials have been performed. Therefore, further large randomized controlled trials with long-term follow-up are needed to prove the positive effects of anti-VEGF therapy for CSC. The studies evaluating anti-VEGF treatment of patients with CSC are summarized in [Table 4].

Mineralocorticoid and Glucocorticoid-Receptor Antagonist

Recently, many studies have investigated the use of MR and glucocorticoid receptor (GR) antagonists for the treatment of CSC worldwide. An increase in endogenous and exogenous corticosteroids was found to be related to CSC, and investigations about the mineralocorticoid pathway, which is a predominant pathway in CSC, have been performed.[41,120] Interestingly, a cross-sectional study of 13 patients with primary hyperaldosteronism demonstrated that retinal abnormalities similar to subclinical CSC were found in patients with primary hyperaldosteronism.[120] According to Zhao *et al*., CSC is correlated with abnormal activation and overexpression of ocular MR, and aldosterone or a high dose of GR increased the expression of water and ion channels on the outer limiting membrane in an animal model, related to the SRF, dilation of the choroid vessels, and leakage.[41] Similar findings have been reported in human Muller glial cell lines.[121] Based on these findings, the authors treated two patients with nonresolving chronic CSC with eplerenone for 5 weeks. These results support the MR signaling pathway as a control for choroidal vasculature, and blockage of MR as a treatment strategy for patients with CSC. Therefore, MR and GR antagonists are expected to alleviate SRF in CSC patients because of an increase in cortisol and dysregulation of endogenous MR.[122]

MR antagonists' spironolactone and eplerenone have been employed in numerous retrospective and prospective studies to treat CSC. The binding affinity for MR was higher for spironolactone than for eplerenone. However, close monitoring of potassium level and renal function should be performed, and cardiac arrhythmia related to hyperkalemia should be considered before using MR antagonists. In addition, systemic side effects can also occur, such as hyperkalemia, hypotension, hypertriglyceridemia, hyponatremia, mastodynia, abnormal vaginal bleeding, and gynecomastia[123,124]

Eplerenone is a specific MR antagonist, used in heart failure management. Eplerenone is associated with a decreased incidence of spironolactone-related adverse events due to its molecular structure, increased selectivity, and fewer side effects related to the activation of progesterone receptors.[125,126] Bousquet *et al*. treated 13 patients with CSC with 25 mg/day of oral eplerenone for a week followed by 50 mg/day for 1 or 3 months. They reported a significant decrease in central macular thickness (CMT) after 1 and 3 months, a significant decrease in SRF after 3 months, and a significant improvement in BCVA.[127] Another prospective, placebo-controlled, double-blinded study randomized 17 patients with chronic CSC to either eplerenone (50 mg/day) or placebo for 3 months. There was no significant difference in SRF and BCVA between the two groups.[128] Additionally, a large-scale, randomized, double-blind, placebo-controlled trial randomized 114 patients with chronic CSC to either eplerenone or placebo. Its result suggested that eplerenone was not superior to placebo.[44] Recently, a multicenter, open-label, randomized controlled spectra trial reported that half-dose PDT is superior to oral eplerenone for chronic CSC patients concerning efficacy outcomes.[129]

Spironolactone is a potassium-sparing diuretic that acts as a competitor for aldosterone. Various studies have confirmed the clinical effects of spironolactone in decreasing CMT, resolving SRF, and improving BCVA in CSC patients.[130-134] Pichi *et al*. performed a prospective, placebo-controlled study to compare treatment with eplerenone and spironolactone in patients with chronic CSC, and concluded that spironolactone was comparable to eplerenone in resolving SRF and statistically superior to eplerenone in improving BCVA. In addition, both were superior to placebo in resolving SRF and improving BCVA.[130] Furthermore, large prospective randomized trials are needed to better estimate the role and clinical efficacy of spironolactone in CSC.

Mifepristone is a high-affinity GR and progesterone receptor antagonist used in gynecological clinical practice.[135] However, few studies have assessed mifepristone in patients with CSC. Thus, more evidence is needed to describe the clinical efficacy of mifepristone.[136,137] The studies evaluating mineralocorticoid receptor antagonist of patients with CSC are summarized in [Table 5].

Conclusion

There are several treatment options for CSC; however, it is challenging in the real world because laser treatment and oral medication are not consistently effective, particularly in

patients with chronic CSC. Because there is poor evidence for anti-VEGF therapy and oral medication, the appropriate treatment of choice for CSC remains controversial. In addition, the definition of the criteria for acute and chronic CSC should be considered, and the nomenclature needs specific modifications and a wider agreement to be implemented in clinical practice and clinical studies. Recently, large multicenter prospective randomized controlled trials were conducted, and, as a result, the treatment outcomes and strategies are gradually evolving. In the future, based on the analysis of more clinical studies, it is expected that the most appropriate treatment methods for patients with CSC will be determined.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initial will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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