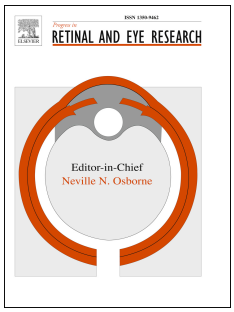

Central serous chorioretinopathy: An evidence-based treatment guideline

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Central serous chorioretinopathy: an evidence-based treatment guideline

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Abstract

Central serous chorioretinopathy (CSC) is a relatively common disease that causes vision loss due to macular subretinal fluid leakage and is often associated with reduced vision-related quality of life. In CSC, the leakage of subretinal fluid through defects in the retinal pigment epithelial layer's outer blood-retina barrier appears to occur secondary to choroidal abnormalities and dysfunction. The treatment of CSC is currently the subject of controversy, although recent data obtained from several large randomized controlled trials provide a wealth of new information that can be used to establish a treatment algorithm. Here, we provide a comprehensive overview of our current understanding regarding the pathogenesis of CSC, current therapeutic strategies, and an evidence-based treatment guideline for CSC. In acute CSC, treatment can often be deferred for up to 3-4 months after diagnosis; however, early treatment with either half-dose or half-fluence photodynamic therapy (PDT) combined with the photosensitive dye verteporfin may be beneficial in selected cases. In chronic CSC, half-dose or half-fluence PDT, which targets the abnormal choroid, should be considered the preferred treatment. If PDT is unavailable, chronic CSC with focal, non-central leakage on angiography may be treated using conventional laser photocoagulation. CSC with concurrent macular neovascularization should be treated with half-dose/half-fluence PDT and/or intravitreal injections of an anti-vascular endothelial growth factor compound. Given the current shortage of verteporfin and the paucity of evidence supporting the efficacy of other treatment options, future studies—ideally, well-designed randomized controlled trials—are needed in order to evaluate new treatment options for CSC.

Abbreviations

aCSC	acute central serous chorioretinopathy
AMD	age-related macular degeneration
BCVA	best-corrected visual acuity
cCSC	chronic central serous chorioretinopathy
CSC	central serous chorioretinopathy
DARA	diffuse atrophic RPE alterations
DRPE	diffuse retinal pigment epitheliopathy
ETDRS	Early Treatment of Diabetic Retinopathy Study
EZ	ellipsoid zone
FA	fluorescein angiography
FAF	fundus autofluorescence
FIPED	flat irregular retinal pigment epithelial detachment
GR	glucocorticoid receptor
HSML	high-density subthreshold micropulse laser
ICGA	indocyanine green angiography
LogMAR	logarithm of the minimal angle of resolution
MNV	macular neovascularization
MR	mineralocorticoid receptor
MTX	methotrexate
Nd:YLF	neodymium-doped yttrium lithium fluoride
NSAID	non-steroidal anti-inflammatory drug
OCT	optical coherence tomography
OCT-A	optical coherence tomography angiography
PAEM	photodynamic therapy-induced acute exudative maculopathy
PCRD	posterior cystoid retinal degeneration
PCV	polypoidal choroidal vasculopathy
PDT	photodynamic therapy
PED	retinal pigment epithelial detachment
RCT	randomized controlled trial
RPE	retinal pigment epithelium
SFCT	subfoveal choroidal thickness
SMARPE	serous maculopathy with absence of retinal pigment epithelium
SMACH	stellate multiform amelanotic choroidopathy
SRF	subretinal fluid
SRT	selective retina therapy

TTT	transpupillary thermotherapy
VA	visual acuity
VEGF	vascular endothelial growth factor

1. Introduction

Central serous chorioretinopathy (CSC) is a chorioretinal disease characterized by a serous neuroretinal detachment in the active disease stage. This neuroretinal detachment is associated with defects in the retinal pigment epithelial layer's outer blood-retina barrier, which occur above corresponding abnormalities in the choroid. Symptoms of CSC typically include impaired and/or distorted central vision together with altered color perception, and the disease is often associated with reduced vision-related quality of life (Breukink et al., 2017a; Sahin et al., 2014). CSC is generally more common among men and has a typical age of onset ranging between 35 and 50 years, although it has been reported to occur as early as 7 years of age and as late as 83 years of age (Castro-Correia et al., 1992; Fine and Owens, 1980; Spaide et al., 1996a; Zhou et al., 2019b). After neovascular age-related macular degeneration (AMD), diabetic macular edema, and retinal vein occlusion, CSC is the fourth most common retinopathy that causes macular fluid leakage (Kido et al., 2021; Kitzmann et al., 2008; Song et al., 2019; Teo et al., 2021; Wong et al., 2014). Although the subretinal fluid (SRF) can resolve spontaneously in CSC, its course can also be complicated, resulting in atrophy of the retinal pigment epithelium (RPE) and/or photoreceptors, as well as secondary macular neovascularization (MNV). Although the pathophysiology of CSC remains poorly understood, choroidal abnormalities appear to play a key role (Brinks et al., 2021a; Cardillo Piccolino et al., 1995; Daruich et al., 2015; Guyer et al., 1994; Kaye et al., 2020; Prunte and Flammer, 1996; Spaide et al., 1996b).

CSC was first described by Von Graefe in 1866 as "relapsing central luetic retinitis" (von Graefe, 1866). In the 1940s, Duke-Elder renamed the condition "central serous retinopathy" (Duke-Elder, 1940). The SRF leakage was subsequently believed to be caused by spasms of the retinal vessels, and in 1955 Bennett was the first to report that patients with central serous retinopathy had a high incidence of stress disorders, stressful life situations, and what he called a "tense obsessional mental make-up" (Bennett, 1955). In 1965, Maumenee observed that CSC was associated with leakage at the level of the RPE, not from the retinal vessels (Maumenee, 1965); a few years later, Maumenee and his colleagues proposed that laser treatment might be effective for treating this leakage (Patz et al., 1971). Subsequently, Gass hypothesized that increased hyperpermeability of the choriocapillaris causes increased hydrostatic pressure, causing retinal pigment epithelial detachments (PEDs) and defects in the RPE outer blood-retina barrier, allowing fluid to leak into the subretinal space (Gass, 1967). This theory was confirmed years later after the introduction of indocyanine green angiography (ICGA) and optical coherence tomography (OCT) (Guyer et al., 1994; Spaide et al., 1996b).

Recently, the incidence of CSC was studied in a population-based longitudinal cohort study using a nationwide database of health insurance claims collected over an 8-year period by the Japanese Ministry of Health, Labour, and Welfare (Kido et al., 2021). The authors found that the incidence of CSC among individuals in the general population 30 years of age and older was 34.0 per 100,000 person-years. Remarkably, they also found that this incidence was nearly 3.5-fold higher in men than

in women (54.2 versus 15.7 per 100,000 person-years, respectively) (Kido et al., 2021). In contrast, a previous population-based study of a predominantly Caucasian population conducted in the US found lower annual age-adjusted rates of CSC in 1980 through 2002, with an incidence of 9.9 and 1.7 per 100,000 men and women, respectively (Kitzmann et al., 2008). Notably, among patients taking oral corticosteroid, an annual incidence of 54.5 and 34.2 per 100,000 men and women, respectively, was reported in a population-based study conducted in Taiwan (Tsai et al., 2014). Another cohort study conducted among users of any type of corticosteroids in South Korea found an incidence of CSC of 54 and 16 per 100,000 person-years in men and women, respectively (Rim et al., 2018). Although these differences in the reported incidence of CSC may be due in part to ethnic, sociodemographic, and/or methodological differences, these rates may be an underestimation. For example, Kitzmann and colleagues excluded patients for whom fluorescein angiography (FA) data were not available (Kitzmann et al., 2008). Moreover, these studies lacked widefield fundus autofluorescence (FAF) imaging, which can reveal otherwise clinically unrecognized gravitational tracts. Lastly, the incidence reported by some studies was based on data regarding insurance claims.

Multimodal imaging modalities, including OCT, FA, ICGA, and FAF, are important for establishing a diagnosis of CSC, as many other conditions can mimic CSC (van Dijk and Boon, 2021). The presence of SRF, as well as increased choroidal thickness, serous PEDs, and dilated choroidal veins, can be evaluated using OCT (Song et al., 2012). FAF can show the extent of associated outer retinal and RPE alterations (Lee et al., 2016a; Spaide and Klancnik, 2005), while FA can detect leakage of fluid into the subretinal space, a characteristic feature of CSC. In addition, choroidal abnormalities characteristic of CSC can be appreciated easily on ICGA (van Rijssen et al., 2021a). Finally, MNV can be detected using a combination of OCT, OCT angiography (OCT-A), FA, and ICGA, although conclusively detecting MNV can be challenging (Borrelli et al., 2018; Ng et al., 2021).

Until recently, the preferred treatment for CSC was somewhat controversial, due to a lack of large prospective randomized treatment trials and relatively few large retrospective studies. Evidence-based treatment of CSC is complicated by a large number of retrospective studies on CSC that do not provide adequate information or lacked sufficient power, including small sample size, no control group, variable and/or questionable inclusion criteria, and inadequate techniques for quantitatively assessing OCT findings (van Rijssen et al., 2018a; van Rijssen et al., 2020a; van Rijssen et al., 2019b). Retrospective studies are particularly problematic in CSC, as spontaneous resolution of SRF is common not only in acute CSC, but even in clinical trials; for example, in the VICI trial 30% of placebo-treated patients with chronic CSC had complete resolution of SRF on OCT after 1 year of follow-up (Lotery et al., 2020). Thus, retrospective studies of CSC have resulted in many scientifically questionable claims regarding treatment efficacy, in which the presumed treatment effect may have been largely due of the disease's waxing-and-waning nature.

In recent years, however, several important steps have been made in order to provide sufficient information to support an evidence-based treatment guideline for CSC. The results obtained from three large, randomized controlled trials (RCTs)—namely, the PLACE trial, the aforementioned VICI trial, and the SPECTRA trial—showed the superiority of half-dose photodynamic therapy (PDT) over high-density subthreshold micropulse laser treatment, non-superiority of the oral mineralocorticoid receptor (MR) antagonist eplerenone treatment compared to placebo, and superiority of half-dose PDT over eplerenone treatment (Lotery et al., 2020; van Dijk et al., 2018b; van Rijssen et al., 2022). In addition, the results of long-term follow-up studies, as well as crossover studies, support the beneficial role of PDT in the treatment of CSC (Chan et al., 2008; Feenstra et al., 2022b; Feenstra et al., 2022c; Park et al., 2021; van Rijssen et al., 2021b; van Rijssen et al., 2020b).

1.1. Clinical characteristics of central serous chorioretinopathy

The classification of CSC remains controversial. Several classification systems for CSC and subtypes of CSC have been proposed, but to date no universal classification has been accepted, ophthalmologists disagree with respect to the classification of CSC (Singh et al., 2019). However, a distinction between acute (aCSC) and chronic (cCSC) forms of CSC is commonly used, based predominantly on the duration of SRF and the structural changes visible on multimodal imaging (Cardillo Piccolino et al., 2005; Guyer et al., 1994). With aCSC, SRF usually resolves spontaneously within 3-4 months, without the need for treatment. In contrast, with cCSC the SRF generally persists for more than 3-4 months, and may lead to permanent structural neuroretinal and RPE damage, as well as subsequent long-term vision loss and decreased vision-related quality of life (Breukink et al., 2017a; Laatikainen, 1994; Loo et al., 2002; Mrejen et al., 2019; von Winning et al., 1982). In addition, some patients with cCSC may report a relatively recent disease onset even though findings on multimodal imaging are indicative of prolonged disease (Mohabati et al., 2018c). Furthermore, in the acute versus chronic CSC classification system, aCSC is often characterized by an isolated dome-shaped neuroretinal detachment on OCT, fewer leakage points on FA, and limited atrophic RPE changes on multimodal imaging (Mohabati et al., 2020a; Wang et al., 2008; Zhao et al., 2015). In contrast, cCSC is distinguished by more extensive leakage on FA, and the chronic leakage of SRF tends to case a shallower neuroretinal detachment compared to aCSC (von Winning et al., 1982). However, some patients with CSC present with one or more leaks on FA that persist for longer than 4 months but are not associated with widespread RPE abnormalities; these cases are therefore difficult to classify using the current aCSC/cCSC classification system. The classification of CSC is discussed in further detail in section 1.1.3.

The term “focal leakage point” typically describes a single point of expanding hyperfluorescence on FA, whereas “diffuse leakage” describes the presence of multiple focal leakage points or ill-defined areas of leakage (Gass, 1967). The leakage of fluorescein through a single defect in the RPE causes a

focal leakage point on early phase FA, which typically increases in size and has indistinct borders in later phases of FA. The focal area of leakage on FA often co-localizes with a corresponding PED visible on OCT. Importantly, a PED is presumed to be the point of least resistance at the RPE outer blood-retina barrier due to increased vascular pressure from the choriocapillaris, which then causes increased wall stress and damage (Daruich et al., 2015; Guyer et al., 1994; Kim et al., 2022b). This small opening in the RPE facilitates leakage into the subretinal space.

Distinguishing between clinical subtypes of CSC is important for determining the optimal treatment strategy. Although the terms aCSC and cCSC are clearly too simplistic to classify CSC adequately, they are widely used in the literature when discussing the disease course and treatment of CSC, and are therefore used in this review as well. Nevertheless, attempts are being made to refine the classification of CSC, for which further validation is needed (see section 1.1.3) (Chhablani et al., 2020; Singh et al., 2019).

1.1.1. Acute CSC

Acute CSC is characterized by a relatively recent onset of serous neuroretinal detachment, often involving the macula (Fig. 1). In most cases, the SRF resolves spontaneously within 3-4 months following onset, and patients with aCSC typically have a good visual prognosis (Daruich et al., 2015; Klein et al., 1974; Nicholson et al., 2013).

A study of 31 patients with aCSC conducted in pre-OCT era showed spontaneous, complete SRF resolution in 84% of cases after 6 months of follow-up (Klein et al., 1974). Another study involving 27 patients with presumed aCSC found that SRF resolved spontaneously in 100% of patients after a mean follow-up of 23 months (Klein et al., 1974). On the other hand, a recurrence of SRF has been reported in up to 52% of patients with aCSC (Ficker et al., 1988; Fok et al., 2011; Mohabati et al., 2020a; Yap and Robertson, 1996). In a retrospective study of 295 affected eyes in 291 patients with aCSC, of which 154 eyes had spontaneous SRF resolution and 141 had SRF resolution after treatment, Mohabati and colleagues found that SRF recurred in 24% of untreated cases and 4% of treated cases (most of which were treated using PDT) (Mohabati et al., 2020a). In addition, some studies have shown that even a brief period of SRF can still cause irreversible photoreceptor damage; thus, relatively early treatment may also be indicated in aCSC cases (Baran et al., 2005; Behnia et al., 2013; Hata et al., 2013).

Several risk factors for prolonged CSC duration at presentation have been proposed, including subfoveal choroidal thickness (SFCT) exceeding 500 µm, PED >50 µm, presentation at 40 years of age or older (Daruich et al., 2017), and photoreceptor atrophy in the area of the detached neuroretina combined with granular debris in the SRF on OCT (Wang et al., 2005). Moreover, a larger volume of SRF in aCSC has been suggested to cause more photoreceptor damage (Gerendas et al., 2018; Nair et

al., 2012). These risk factors, as well as the patient's clinical profile, profession, and preference, can affect the treating physician's choice of whether or not to treat patients with aCSC who present with SRF.

Together with a dome-shaped neuroretinal detachment in aCSC, hyperreflective dots may also be present on FAF and correspond to small white dots visible on ophthalmoscopy. These dots can represent RPE cells, photoreceptor outer segments, and/or macrophages and can migrate progressively into the neuroretina in patients with a prolonged disease course (Spaide and Klancnik, 2005). However, these dots have also been suggested to represent plasma proteins derived from the choriocapillaris and/or inflammatory debris (Wang et al., 2005). Fibrinogen can also leak through the RPE and may—in rare cases—appear on OCT as a presumed fibrin clot (Yu et al., 2014). In addition, a recent study found that patients who present had subretinal fibrin generally had a worse mean baseline BCVA (best-corrected visual acuity) compared to patients without subretinal fibrin (Liang et al., 2021).

In aCSC, up to 1-3 focal leakage points are typically visible on FA. The most common pattern of leakage on FA is described as "inkblot" leakage. This focal leak appears during dye transit and becomes increasingly less-defined as the dye leaks more slowly into the subretinal space through the RPE defect (Wang et al., 2008). Another characteristic leakage pattern on FA in aCSC is known as a "smokestack" leakage (Fig. 1 B, D, and F), which includes a focal hyperfluorescent pinpoint with an expanding area of hyperfluorescence over time. Smokestack leakage on FA can be associated with a larger serous detachment compared to inkblot leakage (Friberg and Karatza, 1997). The location of the focal leakage point is usually correlated with a micro-tear in the RPE, and in aCSC this finding typically occurs in the absence of more diffuse atrophy of the RPE (Daruich et al., 2015).

Areas of focal indistinct hyperfluorescent leakage on ICGA—corresponding to dye leakage due to choroidal vascular hyperpermeability—are characteristic in CSC and are often best visible on mid-phase ICGA. These findings generally correspond to areas in which focal leakage is apparent on FA. In CSC, hyperfluorescent areas on ICGA are generally more widespread than the hyperfluorescent areas on FA, as the primary affected tissue in CSC appears to be the choroid.

With aCSC, areas of decreased autofluorescence on FAF have been found to overlap with attenuation of RPE and areas of leakage on FA (Eandi et al., 2005). Because FAF reflects the functional and structural status of the RPE, this finding is another indicator that the RPE plays a role in the pathophysiology of CSC (Freund et al., 2013; Han et al., 2019). In the absence of significant RPE damage, areas of current or prior SRF typically show as hyperautofluorescence on FAF, due to the increased signal contribution from the RPE.

Some groups consider non-resolving CSC to be a variant of aCSC characterized by persistent SRF lasting at least 4 months with no accompanying RPE abnormalities (Daruich et al., 2015).

Alternatively, recurrent CSC is another variant of aCSC described as one or more episodes of SRF after complete resolution of the first episode of SRF in aCSC (Daruich et al., 2015). However, these variants clearly have clinical overlap, and what may constitute "cCSC" depends largely on the definition used.

Lastly, some cases that appear as aCSC on presentation can develop features consistent with cCSC, making a clear definition and classification system difficult.

1.1.2. Chronic CSC

Chronic CSC is characterized by a persistent serous neuroretinal detachment, which can be either small in size or extensive, as well as multifocal in the case of multiple leakage areas; cCSC typically presents with atrophic RPE changes on FA that can range from a single localized area to extensively DARA (diffuse atrophic RPE alterations), as shown in Fig. 2 (Mohabati et al., 2018c). With cCSC, SRF on OCT typically persists for longer than 3-4 months (Daruich et al., 2015), and one or more focal leakage points are visible on FA. In some cases, clearly identifiable leakage points may be either absent or difficult to identify against the background of irregular RPE "window" defects. The presence of SRF without focal leakage may be indicative of resolving CSC and may appear together with certain signs on OCT such as the so-called "Fuji sign" (an accumulation of SRF on OCT that has the appearance of Mount Fuji in Japan and has been associated with spontaneous resolution) (Feenstra et al., 2022a).

With cCSC, widespread abnormalities on ICGA are typically observed and may include dilated choroidal veins, delayed choroidal filling, and/or choroidal vascular hyperpermeability (Pang et al., 2014). Patients with typical cCSC typically present with one or more areas of indistinct mid-phase hyperfluorescence on ICGA (van Rijssen et al., 2021a).

Although there are currently no strict definitions of severe and non-severe CSC (Mohabati et al., 2018b; Mohabati et al., 2018c), a distinction between complex CSC and simple CSC has been suggested, with complex CSC defined as the presence of a total area of RPE alterations involving an area of more than twice the size of the optic disc diameter. However, to date no conclusive evidence exists to suggest that this definition of complex CSC translates to increased severity in terms of clinical outcome. Interestingly, patients with a history of typical aCSC who present with a severe cCSC phenotype are rare, indicating distinct differences between these disease presentations (Mohabati et al., 2018c). Moreover, with respect to visual outcome the prognosis can differ between aCSC and cCSC. Nonetheless, aCSC, non-severe cCSC, and severe cCSC all appear to have common genetic risk factors (Mohabati et al., 2018a; Mohabati et al., 2020c; Mohabati et al., 2018c; Otsuka et al., 2002) and similarities on multimodal imaging, indicating pathophysiological overlap among these clinical entities (Imamura et al., 2009). Indeed, a retrospective study by Castro-Correia and colleagues

found that up to 50% of patients with unspecified CSC developed atrophic RPE changes within 12 years of presentation (Castro-Correia et al., 1992). In addition, a long-term follow-up study of 61 aCSC cases by Mohabati et al. found that 36% of patients had a tendency toward chronic disease in terms of increased RPE changes over time, while 23% of patients had both an increase in RPE alterations over time and recurrent SRF (Mohabati et al., 2020a).

PEDs on OCT have been reported in 56-96% of affected eyes in patients with CSC (Breukink et al., 2017b; Feenstra et al., 2021; Mitarai et al., 2006; Yang et al., 2013). Virtually all patients with cCSC present with DARA to some extent, possibly due to the prolonged presence of SRF, previous episodes of episodes, or the result of an underlying choroidal dysfunction that directly affects the RPE, similar to pachychoroid pigment epitheliopathy (Cheung et al., 2019; Mohabati et al., 2020b; Mohabati et al., 2018b). Gravitational tracts are defined as areas of RPE and photoreceptor outer segment atrophy, corresponding hyperfluorescent RPE window defects on FA, and mixed hyperautofluorescence and hypo-autofluorescence on FAF that typically extend in the inferior direction to the prominent current or previous points of leakage. Gravitational tracts are believed to develop due to the prolonged presence of SRF. Areas of hyperautofluorescence correspond to a long-standing accumulation of subretinal debris in cases of persistent SRF; in case of a re-attached retina, these areas may correspond to the location of SRF, as this may indicate a loss of photopigments (Spaide and Klancnik, 2005). Hypo-autofluorescent areas on FAF may correspond with the location of SRF accumulation (i.e., shadow artifacts) and/or RPE loss (Han et al., 2020; Imamura et al., 2011; Teke et al., 2014). In addition, granular hypo-autofluorescence on FAF may reflect RPE atrophy (Lee et al., 2016b). With cCSC, the pattern of autofluorescence progresses relatively slowly, as it can take an average of 24 months for granular hypo-autofluorescent changes to progress to confluent hypo-autofluorescence (Zola et al., 2018). When an accumulation of debris from photoreceptor outer segments persists in the subretinal space—possibly after phagocytosis by macrophages—this can appear as increased hyperautofluorescence (Spaide, 2008).

Some patients with cCSC (and some patients with aCSC) who present with more marked and/or extensive atrophic changes in the RPE do not present with a dome-shaped PED, but present with a broader, shallow PED that may have an underlying neovascular component. A neovascular component should be considered when the space between the shallow PED—often referred to as FIPED (a flat, irregular PED) or SIRE (a shallow irregular RPE elevation)—and Bruch's membrane on OCT contains mid-reflective material rather than being hyporeflective, which typically suggests SRF. In addition to these signs on OCT, en face swept-source OCT and OCT-A can be useful for detecting the presence of a secondary MNV—often a type 1 MNV—in combination with FA, and a subtle but visible well-demarcated neovascular structure on ICGA (de Carlo et al., 2015; Ferrara et al., 2014; Soomro et al., 2018; Sulzbacher et al., 2019; Zhang et al., 2023). In a recent retrospective study involving 40 patients with cCSC who presented with evidence of a MNV in one eye, Mandadi et al.

shown that one-fourth of the fellow eyes had a vascular network on OCT-A that was not readily detected on conventional imaging (Mandadi et al., 2021).

In severe cases of cCSC, a complication called posterior cystoid retinal degeneration (PCRD) can occur in which cystoid fluid accumulates in the outer retinal layers (Fig. 3) (Mohabati et al., 2020b; Piccolino et al., 2008). This accumulation of cystoid fluid does not always involve the central macula and is typically located extrafoveally, occurring at various locations in the posterior pole (Piccolino et al., 2008). These cystoid intraretinal spaces may be visible on OCT but—unlike typical cystoid macular edema—do not stain on FA. Thus, PCRD can contribute independently to the loss of central vision in patients with cCSC (Iida et al., 2003; Mohabati et al., 2020b) and is typically associated with long-standing cCSC (Cardillo Piccolino et al., 2008; Mohabati et al., 2020b). Cardillo Piccolino and colleagues studied 34 eyes with cCSC complicated by PCRD and found that BCVA ranged from 20/20 to 20/400, with BCVA 20/40 or better in eyes in which the intraretinal fluid spared the foveal center (Piccolino et al., 2008). In a retrospective study, Sahoo and colleagues detected a MNV on OCT-A in 13 out of 29 cases of CSC with PCRD, but suggested that there may not be a direct correlation between the presence of MNV and PCRD (Sahoo et al., 2019).

Patients with cCSC often experience a gradual decline in both BCVA and contrast sensitivity due to damage to macular photoreceptors (Breukink et al., 2017a; Cardillo Piccolino et al., 2005; Ooto et al., 2010; Spaide et al., 1996a). In up to 13% of eyes with cCSC, this damage can lead to legal blindness, with BCVA reaching 20/200 or worse after 10 years (Mrejen et al., 2019). This decrease in BCVA can be due to changes in foveal atrophic RPE, photoreceptor damage, PCRD, and/or secondary MNV. Indeed, patients with cCSC report decreased vision-related quality of life (Breukink et al., 2017a), and a recent study involving 79 patients with aCSC or cCSC found that the decrease in vision-related quality of life was correlated with disease duration (Karska-Basta et al., 2021). Interestingly, however, three large RCTs found that at presentation vision-related quality of life scores among patients with cCSC were generally high, with mean scores of 81-88 on the 25-item National Eye Institute Visual Function Questionnaire (Lotery et al., 2020; van Dijk et al., 2018b; van Rijssen et al., 2022).

Up to 42% of patients with cCSC present with signs of bilateral involvement on FA, even though most patients present with unilateral visual symptoms (Gackle et al., 1998; Levine et al., 1989). Bilateral CSC is generally more common among patients over 50 years of age, with a prevalence of 50% in this age group compared to 28% of patients under the age of 50 (Spaide et al., 1996a). Bilateral disease activity together with bilateral SRF is more common in severe cCSC phenotypes, present in up to 84% of cases (Mohabati et al., 2018c; Otsuka et al., 2002). Moreover, patients with bilateral severe cCSC have a higher risk of developing severe, irreversible visual impairment (Mohabati et al., 2018c; Mrejen et al., 2019). In some patients, CSC can present in one eye, with another disease in the pachychoroid spectrum presenting in the other eye.

Bullous CSC is a rare form of CSC often complicated by an exudative neuroretinal detachment with shifting SRF (Sartini et al., 2020). In bullous CSC, multiple PEDs are often observed hidden beneath extensive SRF (Sartini et al., 2020), and each PED can evolve into a RPE tear, after which an exudative retinal detachment may develop (Balaratnasingam et al., 2016; Sartini et al., 2020).

Although severe forms of cCSC are typically progressive, the disease course can be slowed—and in turn, BCVA stabilized or even improved with PDT treatment (Mohabati et al., 2018c; Ng et al., 2011).

Finally, in cases of SRF with no clear signs of focal leakage, a wide range of diagnoses other than CSC should also be considered (see Table 1) (van Dijk and Boon, 2021).

1.1.3 Optimizing the classification of CSC

CSC is commonly categorized as either aCSC or cCSC depending on the duration of the presence of SRF and atrophic RPE changes. However, CSC is a complex and variable disease entity that can present as several clinical subtypes; moreover, CSC can present as aCSC, but develop into cCSC over time (Mohabati et al., 2020a). Thus, classifying CSC is extremely challenging. In addition, retina specialists often disagree when describing CSC cases. This high degree of discord among specialists was highlighted in a multicenter study by Singh et al., in which six retina specialists around the globe classified 100 cases of CSC using multimodal imaging data and relevant clinical details (Singh et al., 2019). These six specialists provided 36 different terms to classify the disease, with poor interobserver agreement. In addition, when the authors only considered the three most common descriptors—namely, “acute”, “chronic”, and “recurrent”—they found that the consistency was higher for diagnosing aCSC than for diagnosing either cCSC or recurrent CSC.

In response to the need for a revised CSC classification, the Central Serous Chorioretinopathy International Group recently proposed a new multimodal imaging-based classification system for CSC (Chhablani et al., 2020). This classification includes the following two major criteria, both of which must be met for a diagnosis of CSC: 1) the presence or evidence of a prior serous neuroretinal detachment documented on OCT involving the posterior pole, and unrelated to another disease process; and 2) at least one area of RPE alterations on FAF, spectral-domain OCT, or infrared imaging. In addition to these major criteria, at least one of the following criteria must be met in order to establish a diagnosis of CSC: 1) mid-phase hyperfluorescent placoid areas on ICGA; 2) one or more focal leaks on FA; and 3) SFCT ≥400 μm. Based on these criteria, the authors proposed classifying CSC as either simple or complex, with an area of RPE atrophy twice the size of the optic disc area serving as the threshold for differentiating between these classifications. In addition, they classified CSC cases with a bullous variant, cases with the presence of a RPE tear, and cases associated with another retinal disease as atypical. The two main subtypes—simple CSC and complex

CSC—were further subdivided into three groups, namely primary CSC (defined as the first known episode of SRF), recurrent CSC (defined as the presence of SRF with either a history or signs of resolved episodes), and resolved CSC (defined as the absence of SRF on OCT after a previous finding of SRF). Changes in the outer retinal layer typically seen in long-lasting cases of CSC were also included in this classification system. Because the visual prognosis depends on involvement of the fovea, details regarding foveal involvement—whether in the form of serous neuroretinal detachment, outer retinal atrophy, or serous PED—were also included in the classification system. Lastly, the presence of a CSC-related MNV is also graded, as MNV is a distinct entity and is often associated with a poorer visual prognosis (Bonini Filho et al., 2015; Mandadi et al., 2021).

This novel classification has already been validated in several studies. For example, Chhablani and colleagues provided ten masked retina specialists with clinical details and complete multimodal imaging data for 61 eyes in 34 patients with presumed CSC; these specialists then graded the cases using the above-mentioned classification system (Chhablani et al., 2022). They initially had moderate agreement, with kappa (κ) values of 0.57 (p<0.0001) for the major criteria (after excluding a single outlier observer), and 0.58 for simple CSC, 0.62 for complex CSC, and 0.45 for no CSC. However, they had extremely poor agreement with respect to establishing a diagnosis of atypical CSC (κ=0.008, p=0.8). In a second round of grading, only the images of the fellow eyes were shown in order to determine whether the diagnosis of the affected eye might affect grading of the fellow eye. The authors found that when the grading was performed without prior information regarding the affected eye, the overall kappa value was significantly lower for all groups, and inter-grader agreement was also lower (Chhablani et al., 2022). This finding suggests that the type of CSC diagnosed in one eye is significantly influenced by the history and current state of the fellow eye; thus, disease grading should include both eyes at the same time, although specific grading can be performed separately for each eye. Similarly, Sahoo and colleagues asked two retina specialists to grade 87 eyes in 44 patients with previously undefined CSC (Sahoo et al., 2022). The authors found moderate to strong agreement between all subclassifications, including “simple or complex” (κ=0.91, p<0.001); “primary, recurrent, or resolved” (κ=0.88, p<0.001), and “foveal involvement” (κ=0.89, p<0.001). In addition, Arora and colleagues asked two masked retina specialists to grade multimodal imaging data from 93 patients with CSC and found near-perfect agreement (κ=0.91; 95% CI: 0.8-1.0) for the entire classification (Arora et al., 2021a). Lastly, the same group performed a retrospective observational study involving 229 treatment-naïve eyes with CSC in which multimodal imaging data and clinical information were classified by two retina specialists using this new CSC classification (Arora et al., 2021b). The authors found that both foveal involvement and the presence of outer retinal atrophy were associated with a lower BVCA. Despite these promising results, however, it should be noted that most of these studies (Arora et al., 2021a; Arora et al., 2021b; Sahoo et al., 2022) included only two graders.

In conclusion, to date, this recently proposed classification system dividing CSC into simple versus complex disease is supported, albeit by a relatively small number of validation studies. These encouraging results require further validation—and possible refinement—of this new classification system. Moreover, how these grading systems correspond to patient outcome and/or the need for treatment remains an open question.

1.2 Risk factors for developing CSC

Several risk factors have been associated with CSC. First, studies have shown that men have a 2.7-8 times higher chance of developing CSC compared to women (Haimovici et al., 2004; Tittl et al., 2003; Tittl et al., 1999). In a recent study involving 1,189 male androgen abusers and 11,890 male controls, Subhi and colleagues found no correlation between androgen abuse and an increased risk of CSC, suggesting that biological male sex—and not simply androgen levels *per se*—may underlie the increased risk of CSC in men (Subhi et al., 2023). A particularly high incidence of CSC has been reported in the age group of 35-44 years (Kitzmann et al., 2008; Tsai et al., 2014; Zhou et al., 2019b). The use of corticosteroids is the most significant external risk factor for developing CSC, with odds ratios as high as 37:1 being reported (Haimovici et al., 2004), although lower odds ratios have also been reported (Carvalho-Recchia et al., 2002; Liu et al., 2016a; Rim et al., 2018; Tsai et al., 2014; Zhou et al., 2019b). Although rare, in some cases even minimal exposure to corticosteroids exposure (for example, inhalation, intranasal delivery, or intra-articular injection) has been associated with an increased risk, exacerbation, and/or recurrence of CSC (Carvalho-Recchia et al., 2002; Haimovici et al., 1997), suggesting that the increased risk of developing CSC is not strictly dependent on the dose or mode of corticosteroid administration, but may also depend on genetic predisposition and/or an increased vulnerability to corticosteroid exposure in some individuals.

Interestingly, exhibiting type A behavioral characteristics (i.e., having an intense, sustained drive to achieve self-selected goals, an eagerness to compete, and a desire for recognition and advancement) has been suggested to be associated with CSC (Yannuzzi, 1987). In addition, a “CSC patient profile” has also been hypothesized to increase the risk of developing CSC, and this profile includes a drive to overachieve, impulsiveness, emotional instability, and a hard-driving sense of competitiveness (Conrad et al., 2014). This notion may be plausible, as individuals who exhibit type A behaviors are believed to have increased levels of catecholamines and corticosteroids, which may underlie their apparent increased risk of developing CSC (Williams et al., 1982). Furthermore, stressful life events, engaging in shift work, poor sleep quality, and circadian rhythm disturbances have also been associated with a higher risk of CSC (Bousquet et al., 2016; Gelber and Schatz, 1987; Ji et al., 2018; Setrouk et al., 2016). In addition, several studies found an association between CSS and both certain personality traits and stress (Fok et al., 2011; Kim et al., 2018c; Lahousen et al., 2016; Matet et al., 2017). On the other hand, a recent prospective study by Van Haalen and colleagues did not find an

increased prevalence of cCSC among individuals with maladaptive personality traits such as type A behavioral characteristics compared to a reference group (van Haalen et al., 2019a). However, this group did find that patients with cCSC used certain coping strategies (e.g., seeking social support, passive coping, and active coping in men) more than a reference group (van Haalen et al., 2018a). Furthermore, studies have found that patients with CSC have more psychological problems, a lower quality of life, and higher levels of anxiety compared to healthy controls (Bazzazi et al., 2015; Kim et al., 2018c; Sahin et al., 2014). Nevertheless, large, systematic studies that include detailed psychometric assessments such as suitable, validated questionnaires are needed in order to determine whether a genuine association exists between CSC risk and stress. To date, whether various techniques for reducing stress can have value in the treatment of CSC has not been fully investigated, and the use of extensive stress-reducing measures designed to curb CSC may not be recommended (Nongrem et al., 2021).

Cushing syndrome, a disorder in which the body produces excess levels of cortisol, has also been shown to serve as a risk factor for developing CSC (Abalem et al., 2016; Bouzas et al., 1993; Brinks et al., 2021b; Garg et al., 1997; Gupta et al., 2010; Holtz et al., 2022; Zhou et al., 2019b). Interestingly, some studies found increased serum cortisol levels—although not high enough to establish a diagnosis of Cushing syndrome—in patients with CSC (Haimovici et al., 2003; Kapetanios et al., 1998), whereas other studies did not find increased serum cortisol levels in patients with CSC (van Haalen et al., 2018b). Moreover, CSC may be one of the presenting signs of Cushing disease (van Dijk et al., 2016a). A prospective study by Brinks et al., which included 11 patients with active Cushing syndrome, found retinal abnormalities resembling subclinical CSC in 3 patients (Brinks et al., 2021b). In addition, a recent meta-analysis of macular exam performed in 189 eyes in 159 patients with Cushing syndrome and found CSC in in estimated 7.7% of cases (Holtz et al., 2022). Based on these findings, clinicians should consider referring patients with Cushing syndrome for an ophthalmological exam. Additional support for the putative link between CSC and Cushing syndrome comes from the report that SRF can resolve in patients following surgical treatment for Cushing syndrome, without the need to specifically treat the patient's CSC (van Dijk et al., 2016a). In another study involving 86 consecutive patients with cCSC, elevated 24 h urinary free cortisol levels were measured, suggesting increased activity of the hypothalamic-pituitary-adrenal axis; however, it is important to note that none of the patients with elevated cortisol levels met the clinical or biochemical criteria for Cushing syndrome (van Haalen et al., 2018b). On the other hand, a subsequent study by the same group found that hair cortisol concentrations—a measure of longer-term cortisol levels—were similar between 48 patients with cCSC and 230 population-based controls, with no apparent correlation between hair cortisol concentration and cCSC severity (van Haalen et al., 2019b).

Pregnancy has also been linked to a higher risk of developing CSC, possibly due to choroidal changes induced by abnormal hormone (Sunness, 1988). For example, Kim et al. found no change in choroidal

thickness in women who experience a normal pregnancy; in contrast, they found that pregnant women who develop preeclampsia showed hypertensive changes in the choroidal circulation, including choroidal hyperpermeability and stasis of choroidal vessels (Kim et al., 2016). Another study of 9 women in China found that pregnancy-associated CSC developed predominantly in the third trimester and usually recovered spontaneously following delivery, with ultimately favorable BCVA (Pole et al., 2020; Yu et al., 2021a); these results are consistent with a case report of pregnancy-related CSC (Pole et al., 2020; Yu et al., 2021a). Given that pregnancy has been associated with an increased risk of CSC, women of childbearing age who present with CSC should be asked if they are or might be pregnant, and then monitored closely until delivery (Yu et al., 2021a).

Additional risk factors for CSC have also been suggested and include gastroesophageal conditions such as *Helicobacter pylori* infection, uncontrolled systemic hypertension, use of antibiotics, allergy-based respiratory disease, high socioeconomic status, alcohol consumption, smoking, coronary heart disease, obstructive sleep apnea, poor sleep quality, shift work, autoimmune disease, short axial length, and hyperopia (Bagheri et al., 2017; Chatziralli et al., 2017; Daruich et al., 2015; Eom et al., 2012; Haimovici et al., 2004; Ji et al., 2018; Matet et al., 2017; Nakayama et al., 2021; Oh et al., 2014; Terao et al., 2021; Terao et al., 2020; Tittl et al., 1999; Yavas et al., 2014). In contrast, myopia has been associated with a lower risk of developing CSC (Manayath et al., 2016). It should be noted, however, that these studies are not always consistent with respect to the putative link between these risk factors and CSC; therefore, larger and more rigorous studies are needed.

A familial predisposition to CSC has also been reported in several studies, suggesting that CSC may have a genetic component (Lin et al., 2000; van Dijk et al., 2019; Weenink et al., 2001). Indeed, several single nucleotide polymorphisms (SNPs) have been associated with an increased CSC risk, some of which are located in genes involved in the complement system, including the *CFH* (complement factor H) (de Jong et al., 2015; Hosoda et al., 2018; Miki et al., 2014; Schellevis et al., 2018) and *C4B* (complement factor 4B) (Breukink et al., 2015) genes. Other genes associated with CSC include *NR3C2* (encoding nuclear receptor subfamily 3 group C member 2, a mineralocorticoid receptor) (van Dijk et al., 2017b), *ARMS2 (*age-related macular degeneration susceptibility 2) (de Jong et al., 2015), *CDH5* (cadherin 5) (Schubert et al., 2014), *VIPR2* (vasoactive intestinal peptide receptor 2) (Hosoda et al., 2018), *SLC7A5* (solute carrier family 7 member 5) (Miki et al., 2018; Moschos et al., 2016), *PTPRB* (protein tyrosine phosphatase receptor type B) (Schellevis et al., 2019), as well as the susceptibility loci rs13278062 at *TNFRSF10ALOC389641* and rs6061548 near *GATA5* (GATA binding protein 5) (Hosoda et al., 2019a; Mori et al., 2022). A familial form of pachychoroid possibly inherited in an autosomal dominant pattern has also been reported by Lehmann and colleagues (Lehmann et al., 2015). Finally, genetic studies in Asian and Caucasian patients with CSC showed considerable overlap, specifically in the rs1329428 SNP in *CFH*, the rs13278062 locus at *TNFRSF10A-LOC389641*, and the rs6061548 locus near *GATA5*, indicating that CSC may have

distinct, consistent genetic risk profile regardless of ethnicity (de Jong et al., 2015; Hosoda et al., 2019a; Kaye et al., 2020; Miki et al., 2014).

For an extensive overview of the risk factors associated with CSC, the reader is referred to a recent review by Kaye and colleagues (Kaye et al., 2020).

1.2.1 Risk factors for disease recurrence and disease progression

If left untreated, approximately half (43-51%) of patients with aCSC will develop at least one recurrence (Ficker et al., 1988; Matet et al., 2018; Mohabati et al., 2020a; Ozkaya et al., 2016; Yap and Robertson, 1996), while the 1-year recurrence rate after previous spontaneous resolution in cCSC is 30-52% (Fok et al., 2011; Gilbert et al., 1984). A number of risk factors have been associated with CSC recurrence and progression, including the use of corticosteroids, untreated hypertension, increased SFCT, non-intense hyperfluorescence on FA, shift work, male gender, older age, and sleep disorders (Haimovici et al., 2004; Matet et al., 2018; Yu et al., 2019b). In addition, anxiety disorders and depression have also been suggested to increase the risk and/or recurrence of both aCSC and cCSC (Fok et al., 2011). A study by Hosoda et al. showed that the *CFH* I62V genotype was predictive of spontaneous SRF resolution in patients with active CSC (Hosoda et al., 2019b). Similarly, Kiraly et al. found that patients with CSC with the rs3753394 SNP in the *CFH* gene had an increased tendency for spontaneous SRF resolution at 3 months after disease onset (Kiraly et al., 2021). Moreover, both the *CFH* I62V and *ARMS2* A69S genotypes were significantly associated with MNV development (Hosoda et al., 2019b). A recent study by Yoneyama et al. found a significantly higher frequency of the *CFH* variants rs800292 and rs1329428 in patients with complex CSC (defined as the presence or absence of RPE alterations larger than 2-disc areas in either eye) compared to patients with simple CSC (Yoneyama et al., 2023). Moreover, Singh et al. found that a higher degree of damage in the ellipsoid zone (EZ) within the central 1000 µm of the fovea was associated with a decreased likelihood of SRF resolution (Singh et al., 2020). Lastly, the presence of a Fuji sign has also been associated with spontaneous SRF resolution (Feenstra et al., 2022a). However, all of the aforementioned studies regarding risk factors associated with disease recurrence and/or progression were relatively limited with respect to patient number and/or study design, and further studies are needed in order to confirm these putative associations.

1.3 Pathophysiology

1.3.1. Pachychoroid disease spectrum

The term pachychoroid literally means “thickened choroid” and was used in 2013 in a case series describing mild RPE alterations over areas of thickened choroid (Warrow et al., 2013). This term is

rather nonspecific, as no cut-off point for pachychoroid has been established and can depend on a number of additional factors such as age, axial length, refractive error, and the time of day at which choroid thickness is measured (Brown et al., 2009; Ikuno et al., 2010; Spaide, 2021). In addition, variants in the *CFH* gene have associated with choroidal thickness among some Asian ethnic groups (Fenner et al., 2023). Moreover, many patients who have a thickened choroid do not develop clinically relevant abnormalities or associated diseases considered part of the pachychoroid disease spectrum. In some rare cases, CSC can develop without the presence of pachychoroid (Cheung et al., 2018a; Imamura et al., 2009). Although increased choroidal thickness is a major risk factor for CSC, choroidal dysfunction is another key factor that must be present in the pachychoroid disease spectrum; this is illustrated by the finding that although pachychoroid is usually associated with hyperopia (Ersoz et al., 2018b; Manayath et al., 2016; Terao et al., 2020), typical CSC can still develop in patients with emmetropic or myopic eyes combined with a choroidal thickness that falls within the normal range when refractive error is not considered (Ravenstijn et al., 2021).

The pachychoroid disease spectrum encompasses a number of clinical entities—including CSC—that have specific choroidal abnormalities in common (Cheung et al., 2019; Dansingani et al., 2016; Spaide, 2021; Spaide et al., 2022). These clinical features—which can be appreciated on multimodal imaging—include a diffuse or focal increase in choroidal thickness, "pachyvessels" (dilated choroidal vessels in Haller's layer) together with thinning of the inner choroid overlying these dilated vessels, and choroidal vascular hyperpermeability visible particularly on mid-phase ICGA (Cheung et al., 2018a; Kaye et al., 2020; Spaide et al., 2022). In addition to CSC, the pachychoroid disease spectrum also includes pachychoroid pigment epitheliopathy, peripapillary pachychoroid syndrome (peripapillary choroidal thickening associated with nasal macular intraretinal and/or subretinal fluid, as well as optic disc edema in some cases), pachychoroid neovasculopathy, and pachychoroid-associated polypoidal choroidal vasculopathy (Kaye et al., 2020; Phasukkijwatana et al., 2018; Verma et al., 2021).

The pachychoroid disease hypothesis states that a sequence of events occurs wherein choriocapillaris hyperpermeability (including choroidal dysfunction) is followed by structural changes to the choriocapillaris, RPE complications, and—in some cases—neovascularization either with or without aneurysmal dilatations (Cheung et al., 2019; Siedlecki et al., 2019). However, many patients never progress to symptomatic advanced disease (e.g., extensive atrophic RPE changes, CSC, or neovascularization) with visual impairment. In uncomplicated cases of pachychoroid disease, isolated choroidal changes and thickening of the choroid without visible RPE and/or neuroretinal changes can occur. Although these patients do not yet present with RPE or and retinal abnormalities, ICGA may already show one or more mid-phase hyperfluorescent zones believed be typical of the pachychoroid disease spectrum. Over time, mild atrophic RPE changes can progressively appear; this manifestation is known as pachychoroid pigment epitheliopathy (Warrow et al., 2013). As a disease in the

pachychoroid disease spectrum, CSC is characterized by the presence of SRF leakage causing serous neuroretinal detachment. CSC is commonly associated with a variable degree of atrophic RPE abnormalities and is therefore often preceded by either symptomatic or asymptomatic pachychoroid pigment epitheliopathy, although patients with aCSC may also develop a single focal leak with no associated atrophic RPE changes. Individuals with uncomplicated pachychoroid, pachychoroid pigment epitheliopathy, or non-center-involving CSC are often asymptomatic. The last stage in the pachychoroid spectrum—pachychoroid neovasculopathy—is defined by the presence of a neovascular membrane, primarily in a shallow PED or FIPED as described in section 1.1.2. Pachychoroid neovasculopathy can present with SRF either with or without a known history of CSC, and an associated component of polypoidal choroidal vasculopathy (PCV, also known as "aneurysmal type 1 neovascularization") is not uncommon in these cases and may eventually develop with prolonged disease duration (Cheung et al., 2018a; Fung et al., 2012; Siedlecki et al., 2022). Given the current ambiguity surrounding the term PCV, and to avoid confusion with neovascular AMD, Yamashiro et al. recently suggested using the terms "pachychoroid neovasculopathy without polypoidal lesions" and "pachychoroid neovasculopathy with polypoidal lesions" (Yamashiro et al., 2022). Whether the aforementioned diseases represent bona fide sequential stages in an underlying disease (i.e., "pachychoroid spectrum") is currently unclear; however, several reports have documented the transition from one stage to the next. For example, pachychoroid pigment epitheliopathy has been shown to progress to more advanced stages, including CSC and PCV (Ersoz et al., 2018a; Tang et al., 2022), and patients with CSC can also develop MNV and/or PCV (Peiretti et al., 2018; Peiretti et al., 2015; Peiretti et al., 2019).

1.3.2. Choroidal and scleral dysfunction in CSC

Back in 1967, Gass first suggested that hyperpermeability and increased hydrostatic pressure in the choroid can cause RPE damage, in turn leading to the development of a PED or SRF leakage through a defect in the RPE outer blood-retina barrier (Gass, 1967). Since then, multimodal imaging has shown typical choroidal abnormalities in patients with CSC. These abnormalities often include: one or more areas of focal indistinct hyperfluorescence on mid-phase ICGA (Hayashi et al., 1986; Spaide et al., 1996b; van Rijssen et al., 2021a), which reduces after PDT (van Rijssen et al., 2021a); increased choroidal thickness (Imamura et al., 2009), which can decrease to normal values after PDT (Maruko et al., 2010); dilated veins in Haller's layer; an increased choroidal vascularity index (defined as the ratio between the luminal area and the total choroidal area) (Agrawal et al., 2016a); thinning of the choriocapillaris; and dysregulation of choroidal blood flow (Cardillo Piccolino et al., 2018). The location of the SRF is often correlated with hyperfluorescent abnormalities seen on ICGA, which are believed to reflect vascular hyperpermeability of the choriocapillaris (Prunte and Flammer, 1996;

Teussink et al., 2015; van Dijk and Boon, 2021; van Rijssen et al., 2021a). Moreover, RPE alterations are believed to occur secondary to choroidal changes and dysfunction (Nicholson et al., 2013).

Recently, Spaide and colleagues proposed a novel theory to explain the pathophysiology underlying CSC, noting the important role of choroidal venous overload (Spaide et al., 2022). Using imaging modalities such as ICGA and OCT to visualize the choroidal vasculature, this group and others found venous patterns in CSC eyes that are also seen in eyes following occlusion of the vortex veins and eyes with carotid cavernous fistulas (Fuzzard et al., 2020; Spaide et al., 2022). Eyes with CSC also exhibit choroidal abnormalities such as dilated veins, delayed choroidal filling, choroidal vascular hyperpermeability, imbalanced choroidal venous drainage, and intervortex venous anastomoses (Hiroe and Kishi, 2018; Kishi et al., 2018). Moreover, venous outflow abnormalities such as an abnormal Starling resistor effect appear to be intrinsic to CSC (Spaide, 2020). Notably, arteriovenous anastomoses—direct connections between an artery and a vein that bypass the capillary bed—have also been suggested to play a role in the pathogenesis of CSC (Brinks et al., 2022b).

Studies suggest that congested choroidal outflow, vortex veins, and vascular resistance in CSC and other pachychoroid disease entities are associated with increased scleral rigidity and thickness (Fernandez-Vigo et al., 2021; Imanaga et al., 2021; Lee et al., 2021b; Spaide et al., 2022; Venkatesh et al., 2018a). Interestingly, Sawaguchi and colleagues recently found that the sclera was significantly thinner in eyes with steroid-induced CSC compared to eyes in patients with CSC who did not take steroids (Sawaguchi et al., 2022). Moreover, a recent report by Imanaga and colleagues showed that increased scleral thickness in CSC eyes is significantly correlated with increased choroidal luminal components, providing evidence to support the apparent close relationship between the choroid and sclera in CSC pathology (Imanaga et al., 2023). Furthermore, CSC eyes often present with loculation of fluid in the macula and peripheral ciliochoroidal effusion in association with increased scleral thickness (Imanaga et al., 2022; Spaide and Ryan, 2015; Terao et al., 2022).

Choroidal endothelial cells play an important role in regulating vascular permeability and vascular tone (Nickla and Wallman, 2010; Voigt et al., 2019). The endothelium of the choriocapillaris is fenestrated (Blaauwgeers et al., 1999), allowing for the diffusion of small molecules, as well as molecular exchange between the choroid and retina (Voigt et al., 2019). Corticosteroids play a major role in the risk of developing CSC. Both the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR) have been suggested to have a pathogenic role in CSC. The glucocorticoid cortisol has variety of functional effects throughout the body, and cortisol levels increase in response to stress (Thau et al., 2023). Transcriptional changes induced by cortisol have been measured in endothelial cells in various tissues (Brinks et al., 2018; Brinks et al., 2022a). Interestingly, although GRs have been detected in choroidal endothelial cells, these cells do not appear to express presence of MRs (Brinks et al., 2022a; Brinks et al., 2022c). Consistent with this finding, the MR agonist eplerenone was not superior to placebo when tested as a possible treatment for cCSC in a large RCT (Lotery et

al., 2020). On the other hand, several cortisol-regulated genes have been shown to play a role in endothelial cell function, including *ZBTB16* (zinc finger and BTB domain containing 16), *ANGPTL4* (angiopoietin-like 4), *HIF3A* (hypoxia-inducible factor 3 subunit alpha), *SPARCL1* (SPARC Like 1), and *PLAU* (urokinase-type plasminogen activator) (Brinks et al., 2022a; Voigt et al., 2019). Specifically, cortisol has a marked effect on *ZBTB16* expression, suggesting this gene may play an important role in the pathophysiology of CSC (Brinks et al., 2022a).

As discussed above, a variety of genes have been associated with an increased risk of CSC, including variants in *CFH, C4B, ARMS2, CDH5, NR3C2, PTPRB, SLC7A5, TNFRSF10A,* and *VIPR2* (Kaye et al., 2020; van Rijssen et al., 2019b), some of which may be associated with choroidal endothelial cell function. A variant in the *NR3C2* gene, which encodes the MR, increases the risk of CSC, thus providing a possible genetic basis to explain the putative link between corticosteroids and CSC (van Dijk et al., 2017b). Moreover, variants in the *CFH* and *VIPR2* genes have been associated with increased choroidal thickness (Hosoda et al., 2018; Morino et al., 2022).

Further research is clearly needed in order to unravel the complex pathophysiology of CSC, particularly why men are considerably much vulnerable than women.

1.3.3. Retinal pigment epithelium (RPE) dysfunction in CSC

Although RPE abnormalities are a clinical feature of CSC, the precise role of the RPE in the pathophysiology of CSC is poorly understood. Nevertheless, several hypotheses have been proposed to explain the role of RPE dysfunction in CSC. First, RPE dysfunction may trigger the accumulation of SRF and/or intraretinal fluid, and Negi and Marmor proposed that RPE defects might lead to an outflow of SRF from the choroid (Negi and Marmor, 1984). Subsequently, Spitznas proposed an alternative theory in which a focal loss of RPE cell polarity induces the active transport of SRF to the subretinal space (Spitznas, 1986). However, a large body of evidence suggests that RPE defects occur secondary to choroidal dysfunction, and the choroidal abnormalities present in CSC are usually more extensive then the RPE abnormalities (Spaide et al., 1996b). Interestingly, the unaffected eye in patients with unilateral CSC can also present with RPE abnormalities (Gupta et al., 2010; Warrow et al., 2013), with typical underlying pachychoroid-associated choroidal hyperpermeability on ICGA, indicating that pachychoroid pigment epitheliopathy may in fact be a forme fruste of CSC, resulting from prolonged dysfunction (Ersoz et al., 2018a).

RPE atrophy has been linked to reduced choroidal permeability, which shows as hypofluorescence on ICGA (Spaide et al., 1996b). This change in permeability may be due to progressive remodeling of the choriocapillaris after a long-lasting disease and chronic RPE atrophy, as the release of vascular endothelial growth factor (VEGF) from the RPE is needed to maintain the homeostasis and normal structure of the choriocapillaris (Bhutto and Lutty, 2012). As a result, hydrostatic pressure from the

choroid on the RPE may increase, eventually affecting RPE function and leading to an accumulation of SRF (Gass, 1967; Maruko et al., 2010; Yannuzzi et al., 2003). Secondary damage to the RPE can range from small focal lesions to extensive degeneration, the latter of which has been described using the terms diffuse atrophic RPE alterations (DARA) and diffuse retinal pigment epitheliopathy (DRPE) (Mohabati et al., 2018c; Polak et al., 1995; von Winning et al., 1982; Yannuzzi et al., 1984).

Lastly, as discussed above genome-wide association studies found that the rs13278062 SNP in the *TNFRSF10A-LOC389641* locus is assocated with both AMD and CSC (Arakawa et al., 2011; Fritsche et al., 2016; Hosoda et al., 2019a; Yamashiro et al., 2020). Interestingly, Mori et al. recently studied the functional role of TNFRSF10A in RPE degeneration using human primary RPE cells and *Tnfrsf10* knockout mice (Mori et al., 2022). They found that *TNFRSF10A* was expressed in human RPE cells, and *in vitro* assays revealed that the rs13278062 SNP downregulates *TNFRSF10A* transcription in RPE cells, decreasing cell viability and increasing apoptosis by downregulating protein kinase C-alpha (PKC-α). Based on their findings, the authors suggested that downregulating *TNFRSF10A* expression inactivates PKC-α signaling and increases the vulnerability of RPE cells, thereby contributing to the pathogenesis of AMD and CSC (Mori et al., 2022).

1.4. Differential diagnosis

The differential diagnosis of serous maculopathy includes a broad range of diseases. As many as 13 distinct disease categories associated with—or mimicking—serous maculopathy were recently described by Van Dijk and Boon (van Dijk and Boon, 2021) and include: ocular neovascular diseases, vitelliform lesions, inflammatory diseases, ocular tumors, hematological malignancies, paraneoplastic syndromes, inherited retinal dystrophies, ocular development anomalies, medication-related conditions and toxicity-related disease, rhegmatogenous retinal detachment and tractional retinal detachment, retinal vascular disease, as well as a miscellaneous category that includes serous maculopathy secondary to RPE dysfunction due to confluent drusen, serous maculopathy with absence of RPE (SMARPE) (van Dijk et al., 2022a), serous maculopathy due to aspecific choroidopathy (also described as stellate macular choroidopathy, or SMACH) (Ramtohul et al., 2023). These categories are summarized in Table 1 (van Dijk and Boon, 2021).

Distinguishing between these diseases requires multimodal imaging, often including OCT, OCT-A, FA, FAF, and/or ICGA. In addition to the clinical characteristics such as male preponderance and an age at onset of 20-55 years, several key findings on imaging help differentiate between CSC and other diseases. These findings include: one or more PEDs on OCT; increased choroidal thickness with dilated vessels in Haller's layer (pachyvessels) often associated with a thinned overlying choriocapillaris and RPE changes; focal or multifocal leakage on FA; and—perhaps one of the most typical signs of CSC

712 or pachychoroid disease spectrum—one or more areas of indistinct hyperfluorescence in the affected
713 eye—and often the fellow eye as well—on mid-phase ICGA (Figs. 1 and 2).

714

715

716 **Table 1.**

717 Differential diagnosis of central serous chorioretinopathy.

	Disease	**Clinical characteristics and differential diagnostic aspects**	**Treatment options**	**References**
Peripapillary pachychoroid syndrome	Peripapillary pachychoroid syndrome	Maximal choroidal thickness occurs close to the optic nerve rather than subfoveally, nasal macular intraretinal and/or subretinal fluid and occasional optic nerve edema	Photodynamic therapy, topical steroid	(Cheung et al., 2019; Iovino et al., 2022; Kumar et al., 2022; Phasukkijwatana et al., 2018; Pothof et al., 2023; Spaide et al., 2022)
Ocular neovascular disease	Macular subretinal neovascularization in context of pachychoroid neovasculopathy	Older age, presence of neovascular network on ICGA (sometimes FA), and OCT-A, neovascularization over areas of choroidal thickening and thickened Haller's layer vessels ("pachyvessels")	Intravitreal anti-VEGF injections and/or photodynamic therapy	(Cheung et al., 2019; Pang and Freund, 2015)
	Polypoidal choroidal vasculopathy	Older age; presence of polypoidal dilatations on OCT and ICGA, sometimes with concurrent non-polypoidal neovascularization on ICGA and OCT	Intravitreal anti-VEGF injections and/or (reduced-settings or full-settings) photodynamic therapy	(Cheung et al., 2018a; Cheung et al., 2018b; Coscas et al., 2015; Spaide et al., 1995; Yannuzzi et al., 1990)
	Neovascular age-related macular degeneration	Presence of drusen in combination with or without vitelliform lesion, neovascular lesion on OCT, OCT-A, FA (and ICGA)	Intravitreal anti-VEGF injections	(Bergen et al., 2019; Mehta et al., 2018)
	Other conditions with subretinal neovascularization	- High myopia: chorioretinal atrophy adjacent to optic disc, oblique insertion of optic disc, macular pigment abnormalities, thin choroid - Angioid streaks (often in pseudoxanthoma elasticum): early onset, bilateral deep retinal red-brown bands, optic disc drusen, peripheral round atrophic scars - Multifocal choroiditis: yellow-white punched-out round spots deep to the retina, women < 50 years	Intravitreal anti-VEGF injections	(Aguilar and Green, 1984; Chatziralli et al., 2019; Ikuno, 2017; Kohno et al., 2000; Slakter et al., 1997; Wyszynski et al., 1988)

		- Choroidal rupture: yellow-white subretinal streak, history of blunt eye trauma		
Vitelliform lesions	Autosomal dominant Best vitelliform macular dystrophy and autosomal recessive bestrophinopathy due to *BEST1* gene mutations	Positive family history, symmetrical bilateral disease Vitelliform lesion on fundoscopy centered in the fovea, serous detachment on OCT, filled with hyperreflective material; hyperautofluorescence on FAF; no focal leakage on FA, no choroidal hyperpermeability on ICGA, absent or markedly decreased light rise on electro-oculography Mutations in the *BEST1* gene	No treatment available, intravitreal anti-VEGF injections in case of neovascularization	(Boon et al., 2009b; Boon et al., 2013)
	Acute exudative polymorphous vitelliform maculopathy	Multiple, bilateral well-defined serous macular detachments, subretinal accumulation of yellow-white material; hyperautofluorescence on FAF; no focal leakage on FA/ICGA	No treatment available	(Barbazetto et al., 2018; Gass et al., 1988)
	Adult-onset foveomacular vitelliform dystrophy	Either unilateral or bilateral small (<1 disc diameter) round foveal yellowish subretinal lesions; hyperautofluorescence on FAF; central hypofluorescence with a hyperfluorescent ring on FA (with late staining of vitelliform lesion), either non- or hypofluorescent changes on ICGA	No treatment available	(Chowers et al., 2015; Pierro et al., 2002; Querques et al., 2011; Spaide, 2004)
	Vitelliform lesions secondary to age-related macular degeneration	Presence of drusen in combination with surrounding vitelliform detachment, underlying confluent drusen	AREDS formula supplements (intravitreal anti-VEGF injections in case of neovascularization)	(Bergen et al., 2019; Mehta et al., 2018)
	Vitelliform lesions in the context of other diseases	- Epiretinal membrane - Vitreomacular traction - Persistent SRF after retinal reattachment surgery - Desferrioxamine-related pseudo-vitelliform dystrophy	Either observation or surgical intervention (vitrectomy) for a subset of patients	(Grinton et al., 2021; Querques and delle Noci, 2007; Spaide, 2008)
Inflammatory diseases	Vogt-Koyanagi-Harada disease	Harada disease: only ocular signs, including vitritis and optic disc oedema Rapid onset, young age, bilateral in 95% of cases; cystoid outer retinal fluid on OCT, numerous central leakage points	Corticosteroids, other systemic immunosuppressive medication	(O'Keefe and Rao, 2017; Shin et al., 2015)

		on FA, in some cases with serous inferior retinal detachment; early hyperfluorescence on ICGA, additional signs of anterior and / or intermediate uveitis At least 3 of the following findings to establish the diagnosis Vogt-Koyanagi-Harada disease: bilateral chronic iridocyclitis, posterior uveitis, neurologic signs, cutaneous signs		
	White dot syndromes (e.g., acute posterior multifocal placoid pigment epitheliopathy)	Rapid onset with progressive marked vision loss and often slow recovery, female predominance, relatively young age; (placoid) subretinal (yellow-white) lesions on fundoscopy, OCT, and FA; hypofluorescent changes on late-phase ICGA	Local and/or oral corticosteroids, other systemic immunosuppressive medication (intravitreal anti-VEGF injections in case of neovascularization)	(Birnbaum et al., 2010)
	Posterior scleritis	Middle-aged women; presentation with deep pain, hyperemia of the conjunctiva and large scleral vessels, painful eye movements, choroidal folds, serous retinal detachment, and optic disc oedema on examination; fluid in the sub-Tenon space around the optic disc (T-sign) on ultrasonography, no leakage on FA/ICGA	Corticosteroids, other systemic immunosuppressive medication	(Agrawal et al., 2016b; McCluskey et al., 1999)
	Sarcoidosis	Nodules on conjunctiva and anterior, intermediate, or posterior uveitis on examination, retinal vasculitis, small round atrophic granulomas in inferior peripheral fundus Systemic disease: granulomas in different organs, mainly lungs, skin, and lymphatic system	Corticosteroids, other systemic immunosuppressive medication	(Nunes et al., 2007; Watts et al., 2000)
	Unilateral acute idiopathic maculopathy	Presentation soon after a flu-like illness, young age; swelling of outer retina with elevated and disrupted ellipsoid zone on OCT, spontaneous and quite rapid resolution of SRF; vitritis on examination; no leakage on FA and no hyperfluorescence on ICGA	Observation	(Beck et al., 2004; Freund et al., 1996; Hughes et al., 2012; Yannuzzi et al., 1991)
Ocular tumours	Choroidal naevus and melanoma	Hyperpigmented (sometimes amelanotic) and elevated choroidal mass on fundoscopy; low internal reflectivity on ultrasonography; solid choroidal mass on OCT; multiple	Naevi: regular checks, melanomas may be treated with brachytherapy, proton therapy, or enucleation based on staging	(Higgins et al., 2016; Shields et al., 2019)

		areas of pinpoint leakage on FA (choroidal melanoma), blockage of fluorescence on ICGA Focal leakage on FA may be seen in case of neovascularization	(intravitreal anti-VEGF injections in case of neovascularization, sometimes photodynamic therapy in case of serous SRF leaking from naevus without neovascularization)	
	Choroidal metastases	Yellow-white elevated choroidal lesions, sometimes multifocal and bilateral; minority of patients is not known with a primary tumor at the moment of ocular presentation, high internal reflectivity on B-scan ultrasonography Irregular hyperreflective spots in the photoreceptor layer and RPE layer, in combination with choroidal mass on OCT; early hypofluorescence and late leakage on FA, blockage of choroidal fluorescence on ICGA at the location of the tumor	Observation, chemotherapy, immunotherapy, hormone therapy, whole eye irradiation	(Arepalli et al., 2015; Shields et al., 1997a; Shields et al., 1997b)
	Circumscribed cavernous choroidal hemangioma	Elevated orange-red mass on fundoscopy, elevated choroidal lesion with mixed reflectivity characteristics on OCT that fit within the vascular nature of the tumor, mild diffuse hyperfluorescence on early-phase FA with increasing diffuse leakage throughout the later phases, rapid filling of tumor vessels and late 'wash-out' phenomenon on ICGA, high internal reflectivity on ultrasonography	Photodynamic therapy	(Rahman et al., 2013; Shields et al., 2001)
	Choroidal osteoma	Young women; well-defined bone structure in papillary or macular region; absence of echoes posterior to the tumor on B-scan ultrasonography; hyperreflective horizontal lamellar lines on OCT between choroid and tumor tissue; hyperfluorescent changes on late-phase FA and ICGA	Observation (intravitreal anti-VEGF injections in case of neovascularization)	(Rao and Gentile, 2010; Shields et al., 2015; Shields et al., 2007; Song et al., 2010; Yahia et al., 2008)
Hematological malignancies	Waldenström macroglobulinemia	Bilateral macular serous retinal detachments; no focal leakage on FA, no choroidal hyperpermeability on ICGA, hyperviscosity-related retinopathy on fundoscopy (in some cases)	Chemotherapy, radiotherapy, bone marrow transplantation. No evidence-based effective treatment of retinal lesions.	(Baker et al., 2013; Thomas et al., 1983)

		Overproduction of the monoclonal immunoglobulin type M, blood hyperviscosity		
	Choroidal lymphoma	Presentation between fifth and seventh decade Multifocal, yellow-whitish choroidal infiltrates on fundoscopy, homogenous hyperreflective sub-RPE infiltration (primary vitreoretinal lymphoma) or deep choroidal infiltration (choroidal lymphoma) on OCT	Thorough systemic screening to assess the presence of a systemic lymphoma External beam radiotherapy, intravitreal methotrexate, intravitreal rituximab	(Arias et al., 2013; Barry et al., 2018; Matsuo et al., 1998)
	Leukemia	In majority of patients: cotton wool spots, hemorrhages, vascular tortuosity In minority of patients: bilateral foveal SRF; multifocal granular hyperfluorescence on FA, dot-like choroidal hyperfluorescence without leakage on ICGA Thrombocytopenia, anemia, and leukocytopenia, leukemic blasts in the bone marrow	Chemotherapy, steroids, radiation therapy, stem cell transplantation	(Malik et al., 2005; Moulin et al., 2010)
Paraneoplastic syndromes	Bilateral diffuse uveal melanocytic proliferation (BDUMP)	Several elevated pigmented bilateral uveal lesions and progressive cataract; association with (usually) non-ocular tumors; RPE atrophy and irregularity on examination, early hyperfluorescence on FA, corresponding to the RPE changes and RPE detachments, granular hyperfluorescent changes on ICGA	Plasmapheresis and plasma exchange	(Duong et al., 2006; Gass et al., 1990; Klemp et al., 2017)
	Paraneoplastic vitelliform maculopathy	Relationship with cutaneous and uveal melanoma; vitelliform lesions; anti-RPE and anti-retinal auto-antibodies in serum	No treatment available	(Nagiel et al., 2017; Rahimy and Sarraf, 2013)
Genetic diseases	Best vitelliform macular dystrophy and autosomal recessive bestrophinopathy due to *BEST1* gene mutations	see “Vitelliform diseases”	No treatment available	(Boon et al., 2009b; Boon et al., 2013)

	RP1L1-associated occult macular dystrophy	*RP1L1* gene mutation, autosomal dominant inheritance Poor visual acuity despite very few abnormalities on fundoscopy, thickened and blurry ellipsoid line on OCT in the early stage of disease, which is disrupted and absent in the late phase; few abnormalities on FAF, no focal leakage on FA/ICGA	No treatment available	(Takahashi et al., 2014)
	Central areolar choroidal dystrophy due to *PRPH2* gene mutations	*PRPH2* gene mutation, autosomal dominant inheritance Moderate atrophic RPE changes in stage 1 and 2, geographic atrophy in stage 3 and 4; highly symmetrical FAF abnormalities, no leakage on FA, no hyperfluorescent changes on ICGA	No treatment available	(Boon et al., 2008; Boon et al., 2009a)
	Pseudoxanthoma elasticum and serous fluid	*ABCC6* gene mutation, autosomal recessive inheritance Angioid streaks (bilateral deep retinal red-brown bands radiating from optic disc), thin choroid and Bruch's membrane breaks on OCT; no focal leakage on FA (unless in case of subretinal neovascularization), no CSC-like hyperfluorescent zones on ICGA Localized skin changes ("plucked chicken" appearance), premature atherosclerosis, gastrointestinal and cardiovascular complications	Intravitreal anti-VEGF injections in case of neovascularization	(Hansen et al., 2014; Karampelas et al., 2013)
Ocular developmental anomalies	Dome-shaped macula	Inward macular deviation with a thickened underlying sclera, together with relatively thin choroid, especially on vertical OCT scan, can be associated with SRF	No good evidence on effective treatment	(Caillaux et al., 2013)
	Tilted disc with inferior staphyloma	Anterior position of the upper and temporal portion of the tilted optic disc, oblique axis of the optic disc with an inferonasal crescent-shaped region, mild situs inversus of the retinal vessels, attenuation of the choroid and depigmented RPE in the staphylomatous inferior part of the eye	No good evidence on effective treatment	(Cohen et al., 1998; Nakanishi et al., 2008)

		SRF is visible on horizontal and vertical OCT scan, but vertical OCT scan shows the inferior staphyloma, in which SRF occurs in the watershed zone of thicker to thinner choroid; no focal leakage on FA/ICGA		
	Optic disc pit	Congenital unilateral abnormality of the optic disc (gray "pit") on fundoscopy; no focal leakage on FA, no choroidal hyperpermeability on ICGA; connection of SRF to optic disc and retinoschisis-like intraretinal fluid on OCT	Conservative approach may be preferable in most cases. Treatment is controversial (e.g., juxtapapillary laser photocoagulation, vitrectomy)	(Bloch et al., 2019; Jain and Johnson, 2014)
	Uveal effusion syndrome	Most often in middle-aged hyperopic men; localised areas of RPE hypertrophy and hyperplasia ("leopard spots") on examination, together with peripheral choroidal detachment and sometimes concomitant non-rhegmatogenous retinal detachment with shifting SRF; in the acute phase, 'leopard spots' correspond to hyperfluorescent areas on FA, which later become a mixture of hyperfluorescence and hypofluorescence, early granular hyperfluorescence on ICGA; choroidal detachment on ultrasonography	No good evidence on effective treatment	(Elagouz et al., 2010; Gass and Jallow, 1982; Uyama et al., 2000)
	Focal choroidal excavation with secondary serous subretinal fluid	Concavity in the choroid, with normal overlying retinal architecture	No good evidence on effective treatment	(Chung et al., 2017)
	Macular choroidal macrovessel	Large tortuous choroidal vessel temporally in the macula; no leakage on FA, early filling on ICGA	No good evidence on effective treatment	(Dalvin et al., 2018; Lima et al., 2011)
	Torpedo maculopathy	Hypopigmented lesion of the RPE, temporal to the fovea with a tip pointing toward the fovea, some hyperpigmentation of edges; lack of autofluorescence on FAF and no leakage on FA	No treatment available or necessary	(Roseman and Gass, 1992; Shirley et al., 2018)
Medication-related conditions and toxicity-related disease	MEK inhibitor-associated serous retinopathy (MEKAR)	Onset of SRF associated with MEK inhibitor treatment (targeted treatment for metastatic tumors); bilateral and symmetrical, sometimes multifocal serous retinal detachments, no pachychoroid or RPE detachments on OCT; no leakage on FA; no light rise on electro-oculography	Observation without discontinuation of treatment	(Urner-Bloch et al., 2014; van Dijk et al., 2015)

	Birdshot-like chorioretinopathy associated with checkpoint inhibitors (e.g., pembrolizumab)	Onset of SRF associated with checkpoint inhibitor treatment (for metastatic tumors); macular oedema, retinal vasculitis on examination	Local corticosteroid injections	(Minos et al., 2016; Miyakubo et al., 2019; Obata et al., 2019; Priem and Oosterhuis, 1988; Wong et al., 2012)
	Serous retinopathy caused by hair dye containing aromatic amines (para-phenylenediamine and 5-diamine sulphate)	Similar to MEKAR. Onset of SRF soon after the use of specific commercial hair dye containing aromatic amines; no pachychoroid or RPE detachments on OCT; no leakage on FA and no hyperfluorescent abnormalities on ICGA	Observation	(Faure et al., 2020)
	Poppers maculopathy	Either unilateral or bilateral yellow subretinal (foveal) deposit on fundoscopy, disruption of the ellipsoid zone and slight retinal elevation on OCT, no pachychoroid or RPE detachments on OCT; no leakage on FA	Observation, discontinued use of poppers	(Davies et al., 2012; Rewbury et al., 2017)
Rhegmatogenous retinal detachment and tractional retinal detachment		Acute (or in rare cases gradual) onset of symptoms, such as visual field loss, central vision loss when macula is affected; history of flashes, floaters, and vision loss; pigment in the vitreous, peripheral retinal breaks, and peripheral extension of retinal detachment on examination	Laser photocoagulation, scleral buckling, vitrectomy	(Steel, 2014)
Retinal vascular disease	Diabetic macular oedema	Diabetes mellitus in medical history; other features characteristic of diabetic retinopathy on examination (hemorrhages, microaneurysms, cotton wool spots, hard exudates)	Intravitreal anti-VEGF injections and/or corticosteroid treatment, with or without laser treatment	(Catier et al., 2005; Otani et al., 1999; Ozdemir et al., 2005)
	Retinal vein occlusion	Retinal hemorrhages, cotton wool spots, and vein occlusion on examination; non-perfusion on FA	Intravitreal anti-VEGF injections and/or corticosteroid treatment, with or without laser treatment	(Celik et al., 2016; Gallego-Pinazo et al., 2013)
	Acute hypertensive retinopathy	Retinal hemorrhages, cotton wool spots, and blood vessel occlusion on examination, increased choroidal thickness on OCT in the acute phase	Treatment of hypertension	(Fraser-Bell et al., 2017; Grosso et al., 2005)

		A similar clinical picture may be observed in pregnant women with preeclampsia		
	Pregnancy-related serous maculopathy	Multifocal areas of SRF accumulation on OCT, together with intraretinal cystoid changes and outer retinal changes; hyperfluorescent changes corresponding to dye staining in the subretinal space on FA, choroidal filling defects on ICGA Hypertensive complications of pregnancy (e.g., preeclampsia)	Observation	(Erbagci et al., 2008; Van Rysselberge et al., 2020)
Miscellaneous	Serous maculopathy with absent retinal pigment epithelium (SMARPE)	SRF accumulates due to absence of RPE, no drusen; early hyperfluorescence on FA, no pronounced abnormalities on ICGA	No good evidence on effective treatment	(van Dijk et al., 2022a)
	Serous maculopathy secondary to RPE dysfunction due to confluent drusen	Drusen, signs of AMD/drusen in other eye	AREDS formula supplements (intravitreal anti-VEGF injections in case of neovascularization)	(Cukras et al., 2010)
	Stellate multiform amelanotic choroidopathy (SMACH)	Atrophic RPE changes and hyperpigmentation on fundoscopy, irregular and thickened RPE on OCT, elevated by a thickened and irregular and structurally altered choroid on OCT; early blockage of fluorescein on FA with staining and leakage on mid- to late-phase, variable fluorescence changes on ICGA	No good evidence on effective treatment	(Ramtohul et al., 2023; van Dijk et al., 2022c)

Abbreviations: AMD, age-related macular degeneration; AREDS, Age-related Eye Disease Study; CSC, central serous chorioretinopathy; FA, fluorescein angiography; FAF, fundus autofluorescence; ICGA, indocyanine green angiography; MEK, mitogen-activated protein kinase kinase; MEKAR, MEK inhibitor-associated retinopathy; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; RPE, retinal pigment epithelium; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

2. Treatment for CSC

Determining the optimal treatment for CSC can be challenging due to the wide variety in disease presentation and clinical course, the current lack of consensus regarding a classification system, and the disease's poorly understood pathophysiology (Mehta et al., 2017; Singh et al., 2019). Moreover, some treatment options—particularly PDT—are not available in all countries, and some of treatments may not be covered by the patient's health insurance. The ideal treatment should have a favorable safety profile, particularly given that CSC has a relatively good visual prognosis, even if left untreated in many cases. Importantly, the inclusion and exclusion criteria, study endpoints, and clinical definitions vary among retrospective studies regarding the treatment of CSC (van Rijssen et al., 2018a). The relatively high rate of spontaneous SRF resolution in aCSC—and in up to 30% of cCSC cases (Lotery et al., 2020)—may explain the apparent promising results reported for a range of treatments studied in non-systematic, non-prospective, non-randomized studies, but these results have not been replicated by sufficiently powered prospective RCTs. If a study is not properly designed—for example, by lacking a suitable control group—the researchers may reach the potentially false conclusion that the treatment was effective, particularly if they fail to take into account spontaneous improvement (van Rijssen et al., 2020a). However, three large investigator-initiated multicenter RCTs for the treatment of cCSC were recently published (Lotery et al., 2020; van Dijk et al., 2018b; van Rijssen et al., 2022). These studies and a number of other RCTs helped to establish an evidence-based treatment guideline for CSC based on currently available data.

2.1 Aims of treatment

The ultimate goal in treating CSC is to achieve complete SRF resolution, thereby preserving the outer neurosensory retinal layers, as even a small amount of persistent SRF can lead to irreversible damage (Haga et al., 2017; Loo et al., 2002; van Rijssen et al., 2018a). To restore the normal photoreceptor-RPE interaction, complete SRF resolution should therefore be one of the primary endpoints in intervention trials regarding the treatment of CSC. Patients with CSC often have a gradual improvement in visual symptoms and visual function after the photoreceptor-RPE interaction is restored (van Rijssen et al., 2018a). However, even after successful treatment (i.e., complete resolution of SRF), visual symptoms can persist due to preexisting irreversible neurosensory retinal and/or RPE damage (Wong et al., 2004), and these symptoms can include suboptimal BCVA, loss of contrast and/or color vision, and metamorphopsia. Nevertheless, an intriguing question is why the visual prognosis is generally much better with subfoveal SRF associated with CSC compared to subfoveal SRF associated with a rhegmatogenous retinal detachment.

In addition to complete SRF resolution, another important goal in the treatment of CSC is to preventing recurrence and future disease progression.

2.2 Elimination of risk factors

In addition to actively treating CSC, eliminating potential risk factors can play an important role in improving the treatment of CSC, regardless of the subtype of CSC. For instance, patients with CSC should be advised to discontinue the use of all forms of corticosteroids, provided that this is clinically feasible (Loo et al., 2002). Patients who present with one or more symptoms suggestive of Cushing disease such as abdominal obesity, abdominal stretch marks, muscle weakness, easy bruising, facial rounding and flushing, osteoporosis, hypertension, diabetes mellitus, the presence of dorsal fat pads, and/or neuropsychiatric symptoms should be referred to an endocrinologist (Brinks et al., 2021b; van Haalen et al., 2018b). Notably, ophthalmologists should be aware that in some patients CSC can serve as the primary presenting feature of Cushing disease, as the symptoms listed above can be very subtle (van Dijk et al., 2016a).

2.3 Treatment options for CSC

2.3.1. Photodynamic therapy (PDT)

Although PDT was originally developed as a treatment for skin cancer (Daniell and Hill, 1991), it has now used in ophthalmology for over two decades (Group, 1999; Miller and Miller, 1993; Miller et al., 1991; Miller et al., 1995; Yannuzzi et al., 2003). For example, the light-sensitive compound verteporfin is approved for use in PDT for the treatment of MNV caused by either AMD or pathological myopia. Verteporfin has also been used as an off-label treatment for CSC, particularly cCSC (Newman, 2016). Verteporfin binds to plasma low-density lipoproteins, which then bind to surface receptors on vascular and reticuloendothelial cells (Schmidt-Erfurth and Hasan, 2000). The therapeutic effect of PDT is believed to be based on the release of free radicals when the treatment site is illuminated in association with the photosensitizing dye, and this effect is primarily activated in the choriocapillaris. This may then be followed by remodeling of vessels in the capillary bed in the vascular endothelium. Because of the high selectivity of verteporfin for choroidal blood vessels, retinal photoreceptors are not affected by PDT (Chan et al., 2003; Schlotzer-Schrehardt et al., 2002), and the risk of damage to the RPE is also low (Feenstra et al., 2023; Schmidt-Erfurth and Hasan, 2000). PDT for the treatment of CSC has been extensively studied since the first report of its use in this condition, and studies to date regarding PDT in CSC with at least 50 patients with CSC are summarized in Table 2.

788 **Table 2.**

789 Overview of studies involving at least 50 patients with central serous chorioretinopathy treated using photodynamic therapy (PDT).

Study	CSC subtype	Study design	Mean age (years)	PDT setting	Number of eyes	Follow-up (months)	Complete SRF resolution at last follow-up (%)	Reported parameters and outcomes
(Chan et al., 2008)	aCSC	Prospective randomized controlled trial	41	ICGA-guided half-dose	63 eyes (63 patients)	12	95% (PDT), 58% (placebo)	Mean LogMAR BCVA improved from 0.16 to -0.05 in the half-dose PDT group, compared to 0.11 at baseline to 0.05 at 12 months in the placebo group.
(Zhao et al., 2015)	aCSC	Non-inferiority double-masked randomized controlled clinical trial	43	FA-guided half-dose or 30% dose	131 eyes (131 patients)	12	75% (30% dose group), 95% (half-dose group)	Mean ETDRS BCVA improved from 75 to 83 letters in the 30% dose group, and from 75 to 85 letters in the half-dose group.
(Alkin et al., 2014)	cCSC	Retrospective study	45 (low-fluence group), 44 (half-dose group)	ICGA-guided half-fluence or half-dose	36 eyes (34 patients in half-fluence group), 28 eyes (26 patients in half-dose group)	13 (mean)	92% (half-fluence group), 93% (half-dose group)	Mean ETDRS BCVA increase of 7 letters in half-fluence group, and 5 letters in half-dose group.
(Breukink et al., 2016a)	cCSC	Retrospective case–control study	55 (corticosteroid users), 54 (controls)	ICGA-guided half-dose or half-time	35 eyes (33 corticosteroid users), 88 eyes (84 control patients)	11 (mean in corticosteroid group, 12 (mean in control group)	74% (corticosteroid-associated CSC group group), 60% (CSC group without corticosteroid use)	Mean ETDRS BCVA at final follow-up visit was comparable between the corticosteroid-associated CSC group and the control group (72 and 71 letters, respectively).
(Chung et al., 2018)	cCSC	Case series	51	ICGA-guided half-dose	61 eyes (52 patients)	3	88%	Mean LogMAR BCVA improved from 0.47 to 0.31 at 3 months.
(van Dijk et al., 2018b)	cCSC	Open-label, multicenter randomized controlled clinical trial	49	ICGA-guided half-dose	89 eyes (89 patients)	7–8	67%	Mean ETDRS BCVA improvement of 7 letters, mean retinal sensitivity improvement of 3 dB on microperimetry.
(Fujita et al., 2015)	cCSC	Retrospective interventional case series	53	ICGA-guided half-dose	204 eyes (204 patients)	12	89%	Mean LogMAR BCVA improved from 0.11 to −0.01.
(Haga et al., 2017)	cCSC	Retrospective observational case series	52	ICGA-guided half-dose	79 eyes (73 patients)	36	81%	Mean LogMAR BCVA improved from 0.21 to 0.08.

(Hua et al., 2018)	cCSC	Retrospective study	Not specified	FA- or ICGA-guided one-third dose, full-fluence	68 eyes (60 patients)	6 (median of 8)	6 months: 93%	SFCT of affected eyes changed from 381 μm before treatment to 375 μm at 6 months. Mean LogMAR BCVA improved from 0.62 at baseline to 0.21 at 6 months.
(Iovino et al., 2020)	cCSC	Retrospective multicenter cohort study	51	ICGA- or FA-guided half-dose or half-fluence	81 eyes (77 patients; 30 eyes half-dose and 51 eyes half-fluence)	3	44% (1 month after treatment), 61% (3 months after treatment)	Mean LogMAR BCVA improved from 0.39 at baseline to 0.29 at 1 month, and 0.25 at 3 months. SFCT decreased from 430 μm at baseline to 395 μm at 1 month and 398 μm at 3 months.
(Karasu and Yucel, 2021)	cCSC	Retrospective study	45	ICGA-guided half-fluence or half-dose	30 eyes (30 patients in half-fluence group), 30 eyes (30 patients in half-dose group)	12	50% (half-fluence group), 67% (half-dose group)	Mean LogMAR BCVA increased from 0.69 at baseline to 0.20 at 12 months in the half-fluence PDT group. SFCT decreased from 275 μm at baseline to 236 μm at 12 months. In the half-dose PDT group, mean LogMAR BCVA increased from 0.66 at baseline to 0.17 at 12 months. SFCT decreased from 274 μm at baseline to 255 μm 12 months.
(Kim et al., 2015d)	cCSC	Retrospective study	47	ICGA-guided half-fluence or half-dose	57 eyes (52 patients)	34 (mean)	72%	PDT resulted in a significant improvement of BCVA and a significant reduction in SFCT.
(Kim et al., 2015e)	cCSC	Retrospective study	47	ICGA-guided half-fluence or half-dose	52 eyes (52 patients)	21 (mean in half-fluence group), 22 (mean in half-dose group)	96%	Complete photoreceptor recovery, defined as a continuous ellipsoid zone with a discernible interdigitation zone, was observed in 19 (73%) and 14 patients (54%) in the half-fluence and half-dose PDT groups, respectively.
(Lai et al., 2015)	cCSC	Retrospective study	45	ICGA-guided half-dose	75 eyes (75 patients)	69 (mean)	93%	Mean LogMAR BCVA improved from 0.35 to 0.14 at 3 years after treatment.
(Lai et al., 2016)	cCSC	Retrospective multicenter interventional case series	49	ICGA-guided half-dose	136 eyes (123 patients)	58 (mean)	97% (at 36 months after treatment)	Mean LogMAR BCVA improved from 0.36 to 0.15 at 36 months.
(Lim et al., 2014)	cCSC	Retrospective case series	52	ICGA- or FA-guided full- or reduced-settings	265 eyes (237 patients)	1–12 (range)	81%	Mean changes in LogMAR BCVA from baseline were -0.5, -0.14, and -0.23 for eyes with baseline Snellen BCVA of 20/32, 20/40 to 20/80, and 20/100, respectively.
(Nicolo et al., 2014)	cCSC	Retrospective study	49	Half-fluence or half-dose Guidance system not specified, but targeted to the	31 eyes (28 patients in half-fluence group), 29 eyes (28 patients in half-dose group)	12	84% (half-fluence group), 100% (half-dose group)	Mean LogMAR BCVA improved significantly, in half-fluence group (from 0.187 to 0.083 and in half-dose group (from 0.126 to 0.068).

				area of choroidal hyperpermeability				
(Noh et al., 2019)	cCSC	Retrospective study	53 (focal PDT group, 55 (conventional PDT group)	ICGA-guided full-dose PDT, either focal (covering only the localized hyper-fluorescent area on ICGA) or conventional (covering the total area of abnormal choroidal vessels including the leakage point)	26 eyes (26 patients in focal PDT group), 26 eyes (26 patients in conventional PDT group)	12	100% (both groups)	Mean SFCT decreased from 335 and 348 μm at baseline to 263 and 272 μm at 12 months in the focal PDT group and conventional PDT group, respectively.
(Park et al., 2019b)	cCSC	Retrospective study	48	ICGA-guided half-fluence or half-dose or standard	76 eyes (73 patients in half-fluence group), 12 eyes (half-dose group), 6 eyes (standard group)	58 (mean)	77% SRF resolution (at 1 month after treatment)	Mean LogMAR BCVA improved from 0.55 at baseline to 0.19 at final visit.
(Park et al., 2021)	cCSC	Prospective randomized comparative consecutive open-label clinical trial	51 (30%-fluence), 49 (40%-fluence), 55 (50%-fluence)	ICGA-and FA-guided 30%-fluence, 40%-fluence or 50%-fluence	15 eyes (15 patients in 30%-fluence group), 16 eyes (16 patients in 40%-fluence group), 17 eyes (17 patients in 50%-fluence group)	12	60% (30%-fluence group), 81% (40%-fluence group), 100% (50%-fluence group) The recurrence rate in the 50%-fluence group was lower than that in the 30%- and 40%-fluence groups at 12 months (30% vs. 50%, 40% vs. 50%; p=0.002, p=0.030, respectively.	Mean LogMAR BCVA changed in the 30%-, 40%- and 50%-fluence PDT group from 0.33, 0.32, and 0.28 at baseline, to 0.19, 0.17, and 0.07 at 12 months, respectively. Mean SFCT decreased in the 30%-, 40%-, and 50%-fluence groups from 397, 384, and 425 μm at baseline, to 266, 266, and 239 μm at 12 months.
(van Rijssen et al., 2022)	cCSC	Prospective randomized controlled trial	45	ICGA-guided half-dose	53 eyes (53 patients)	3	78%	Mean ETDRS BCVA improved from 78 letters at baseline to 84 letters at 3 months. The retinal sensitivity on microperimetry improved from 23 dB at baseline to 25 dB at

								3 months. The NEI VFQ-25 score improved from 82 to 87 points.
(Roca et al., 2018)	cCSC	Retrospective study	47	ICGA-guided half-dose	68 eyes (68 patients)	12	95%	Mean LogMAR BCVA improved from 0.50 to 0.47.
(Ruiz-Moreno et al., 2010)	cCSC	Non-randomized multicenter interventional case series	46	FA-guided full-settings	82 eyes (72 patients)	12 (mean)	100%	Mean LogMAR BCVA improved from 0.53 to 0.37.
(Scholz et al., 2016)	cCSC	Retrospective study	53	ICGA- and FA-guided half-dose	58 eyes (58 patients)	1.5	21%	Mean LogMAR BCVA improved from 0.35 at baseline to 0.31 at 6 weeks.
(Sheptulin et al., 2018)	cCSC	Retrospective case series	49 (median)	ICGA- or FA-guided half-time	114 eyes (103 patients)	12	87%	Median improvement of LogMAR BCVA from 0.22 to 0.1.
(Shin et al., 2011)	cCSC	Retrospective study	48 (half-fluence group), 51 (full-fluence group)	FA-and ICGA-guided full-fluence or half-fluence	34 eyes (29 patients in half-fluence group), 33 eyes (31 patients in full-fluence group)	13 (mean)	94% (half-fluence), 100% (full-fluence)	There was no difference in final mean LogMAR BCVA between the 2 groups (0.17 versus 0.21.
(Son et al., 2019)	cCSC	Retrospective study	49	ICGA-guided full-fluence or half-fluence	37 eyes (37 patients in full-fluence group), 30 eyes (30 patients in half-fluence group)	36	100%	Mean LogMAR BCVA improved from 0.34 and 0.36 at baseline to 0.15 and 0.15 at 36 months in the full-fluence and half-fluence group, respectively. The SFCT decrease significantly in both the full-fluence and the half-fluence group, from 416 µm and 410 µm at baseline to 317 µm and 349 µm at 36 months.
(Tseng and Chen, 2015)	cCSC	Retrospective interventional case series	45	ICGA-guided half-dose	56 eyes (56 patients)	56 (mean)	100% (at 12 months)	Mean LogMAR BCVA improved significantly from 0.36 to 0.13 at 6 months after treatment.
(Hayashida et al., 2020)	CSC (presence of foveal SRF on OCT for at least 3 months)	Retrospective study	53 (-FA-guided PDT group), 55 (ICGA-guided PDT group)	ICGA- or FA-guided half-time	29 eyes (29 patients in FA-guided PDT group), 32 eyes (32 patients in ICGA-guided PDT group)	12	97% (FA-guided PDT), 100% (ICGA-guided PDT)	Mean LogMAR BCVA improved from 0.058 to -0.065 at 12 months in the ICGA-guided group compared to 0.026 to -0.064 in the FA-guided PDT group. Persistent or recurrent SRF was seen in 34% of the patients who received FA-guided PDT compared to 13% of the ICGA-guided treated patients.

(Li et al., 2022)	CSC, not specified	Retrospective study	47	ICGA-guided half-dose	150 eyes (143 patients)	3	83%	Mean LogMAR BCVA was 0.46, which improved to 0.35 at last follow-up. Mean ONL thickness was 90 μm at baseline and was 89 μm at last follow-up.
(Liang et al., 2021)	CSC, not specified	Retrospective study	47	ICGA-guided half-dose	173 eyes (153 patients; 48 eyes with subfoveal fibrin, 125 eyes without subfoveal fibrin)	6	92% (fibrin group), 84% (non-fibrin group)	There was no statistically significant difference between the 2 groups in terms of improvement in BCVA at each follow-up visit (1 month: p=0.069; 3 months: p=0.111; 6 months:, respectively).
(Liu et al., 2016b)	aCSC or cCSC	Retrospective case series	46	FA-guided, half-dose or half-time	35 eyes (35 patients in half-dose group), 26 eyes (26 patients in half-time group)	12	91% (half-dose group), 100% (half-time group)	Mean LogMAR BCVA improved from 0.39 to 0.14 in the half-dose group and from 0.29 to 0.14 in the half-time group.
(Mohabati et al., 2018b)	Severe cCSC	Retrospective study	49 (severe cCSC), 47 (controls)	Half-dose or half-time Guidance system: not specified	81 eyes (66 patients in severe cCSC group), 37 eyes (35 patients in control group)	21 (mean)	88% (severe cCSC group), 95% (control group)	Mean ETDRS BCVA improved from 66 to 72 letters in the severe cCSC group, and from 78 to 82 letters in the control group.
(Penas et al., 2021)	aCSC and cCSC (63% of eyes shows signs of chronicity)	Retrospective study	49	Half-dose Guidance system: not specified	111 eyes (95 patients)	35 (mean)	94% (at 3 months)	Mean BCVA improved significantly compared to baseline, was registered in every visit until 60 months post-treatment until 24 months. Central retinal sensitivity on microperimetry significantly improved in the 4º, 12º and 20º central field until the 24 months visit.
(Yamada-Okahara et al., 2023)*	Persistent CSC	Retrospective study	52	FA- and ICGA-guided half-fluence	41 eyes (41 patients)	3	81%	No significant changes in BCVA.
(Yu et al., 2019a)	CSC, not specified	Retrospective study	45	ICGA- or FA half-dose	62 eyes (62 patients)	12	(Only patients with complete SRF resolution within 2 months after PDT were included)	Mean LogMAR BCVA improved from 0.30 at baseline to 0.06 at 12 months.
(Yu et al., 2021b)	CSC, not specified	Retrospective study	45	ICGA- or FA-guided half-dose	132 eyes (132 patients)	12	Of the 663 eyes from 583 patients with CSC who underwent half-dose PDT, 90% had complete SRF resolution at 2 months.	Mean LogMAR BCVA improved from 0.33 at baseline to 0.12 at 12 months.

							(Only patients with a SRF resolution within 2 months of PDT were included)	
(Wakatsuki et al., 2021)	Persistent CSC (more than 4 months of SRF duration)	Retrospective study	54	Half-dose Guidance system: not specified	140 eyes (140 patients)	3	85% (complete SRF resolution in the macula)	Mean ETDRS BCVA improved from 78 at baseline to 82 at 3 months. The SFCT decreased from 378 µm at baseline to 323 µm at 3 months.

aCSC, acute central serous chorioretinopathy; BCVA, best-corrected visual acuity; cCSC, chronic central serous chorioretinopathy; CSC, central serous chorioretinopathy; dB, decibel; ETDRS, Early Treatment of Diabetic Retinopathy Study Letters; FA, fluorescein angiography; ICGA, indocyanine green angiography; LogMAR, logarithm of the minimal angle of resolution; NEI-VFQ-25, National Eye Institute Visual Functioning Questionnaire 25-item version; OCT, optical coherence tomography; ONL, outer nuclear layer; PDT, photodynamic therapy; SFCT, subfoveal choroidal thickness; SRF, subretinal fluid.

*Due to the optimal design and aCSC population, this study was included here even though it included patients fewer than 50 patients.

2.3.1.1 Treatment algorithms and mode of action

In the first studies evaluating the potential of using PDT as a treatment for CSC, either "standard" or "full" settings—similar to the settings typically used for the treatment of neovascular AMD—were used. The standard settings include a verteporfin dose of 6 mg/m^2, 689-nm wavelength laser light delivered at 50 J/cm^2 fluence at an intensity of 600 mW/cm^2, and a treatment time of 83 seconds (Group, 1999). To avoid the potential though rare complication of profound ischemia in the choroid—as observed on a few occasions following PDT for neovascular AMD (Rishi et al., 2011; Wachtlin et al., 2003)—several alternative PDT regimens have been described using reduced treatment settings such as reducing the verteporfin dose by half (3 mg/m^2 instead of 6 mg/m^2), using half fluence (25 J/cm^2 instead of 50 J/cm^2), and/or half of the original treatment time (42 seconds instead of 83 seconds) (Alkin et al., 2014; Neves et al., 2016; Shin et al., 2011; Shiode et al., 2015; van Rijssen et al., 2019b).

Before performing PDT, the target area to be irradiated with a circular spot of light must be properly selected (Figs. 4 and 5) (van Dijk et al., 2020). The target area is often set so that the diameter of this spot covers the hyperfluorescent area(s) on mid-phase ICGA and the corresponding point(s) of leakage on FA and OCT (van Dijk et al., 2018b; van Dijk et al., 2020; Yannuzzi et al., 2003). Currently, ICGA-guided PDT is more common than FA-guided PDT, which used to be the standard. Using ICGA to target the choroidal abnormalities with the PDT laser spot can help ensure that the underlying choroidal abnormalities are treated with maximum efficacy. The macula should be treated first, immediately followed by additional treatment spots, if needed. Whether several spots can overlap during the treatment regimen is an open question. Prior to PDT, the pupil should be dilated using a topical mydriatic agent, followed by either 6 mg/m^2 (full-dose) or 3 mg/m^2 (half-dose) verteporfin delivered via an intravenous infusion over a period of 10 minutes. An anesthetic eye drop (e.g., oxybuprocaine 0.4%) is then administered, a contact lens (typically a 1.6x magnification PDT lens) is positioned on the eye, and treatment is performed with 15 minutes after the start of verteporfin infusion. For full-fluence PDT, light at 689 nm with a fluence of 50 J/cm^2 is applied for 83 seconds to the designated area. In the case of half-fluence PDT in combination with full-dose verteporfin (6 mg/m^2), a fluence of 25 J/cm^2 for 83 seconds is used. Lastly, half-time PDT may also be used, which includes full-dose verteporfin (6 mg/m^2), full-fluence (50 J/cm^2), for a treatment time of 42 seconds. After treatment, patients should be advised to avoid exposure to direct sunlight and other sources of UV radiation (particularly 689-nm wavelength light), as patients remain photosensitive for up 48 hours after treatment, even with half-dose PDT (van Dijk et al., 2020). Importantly, half-dose PDT has been shown to be equally effective as—or even superior to—full-dose, half-fluence, and half-time PDT regimens for the treatment of both aCSC and cCSC (Liu et al., 2016b; Shiode et al., 2015). Half-dose PDT may be preferred over half-fluence and half-time PDT, for several reasons. First, more prospective and sufficiently powered retrospective data support the efficacy of half-dose PDT

compared to other treatment regimens. Second, half-dose PDT may have a reduced risk of photosensitivity due to the lower dose of systemic verteporfin. Finally, using half the verteporfin dose per patient means that a single-dose vial of verteporfin can be used to treat two patients, which reduces treatment cost and can increase verteporfin availability in times of shortage (Sirks et al., 2022); however, in some countries such as the US, using one vial to treat two patients can be problematic and can have legal consequences with respect to insurance billing.

Choroidal thickness may temporarily increase following half-dose PDT for CSC (Maruko et al., 2010), and this transient choroidal thickening can be accompanied by a temporary increase in SRF, with worsening of visual symptoms lasting up to 4 weeks reported in up to 38% of PDT-treated patients (Fernandez-Vigo et al., 2022; Maruko et al., 2010; van Dijk et al., 2018a). These treatment-related changes generally improve within 1-3 weeks after PDT, with gradual improvements in anatomical and functional outcome (Maruko et al., 2011; van Dijk et al., 2018a; van Dijk et al., 2018b; van Rijssen et al., 2022). In patients with unilateral CSC, choroidal thickness in the treated (i.e., affected) eye can decrease to the same thickness as the fellow (i.e., unaffected) eye (Izumi et al., 2017; Maruko et al., 2011; Pryds and Larsen, 2012), suggesting that PDT can reduce choroidal thickness to relatively normal levels. In addition, PDT has been shown reduce choroidal hyperpermeability and leakage on ICGA (Maruko et al., 2010; van Rijssen et al., 2021a). Studies regarding PDT for the treatment of CSC often include more patients with cCSC and fewer patients with aCSC, as spontaneous resolution is more common in aCSC (Klein et al., 1974). Two studies found no significant difference between half-fluence PDT and half-dose PDT with respect to outcome for the treatment of cCSC (Alkin et al., 2014; Karasu and Yucel, 2021), although another study found that half-dose PDT led to earlier complete SRF resolution compared to half-fluence PDT measured at the 1-month follow-up visit (Nicolo et al., 2014). In a retrospective study, Park et al. compared full-dose, half-dose, and half-dose/half-fluence PDT and found that both full-dose and half-dose PDT were effective in terms of significantly improving BCVA, whereas the half-dose/half-fluence PDT had no significant effect (Park et al., 2019a). Other studies found similar efficacy between half-fluence PDT and full-fluence PDT for the treatment of cCSC (Boni et al., 2012; Shin et al., 2011; Son et al., 2019), although a retrospective study by Son et al. found that patients treated with full-fluence PDT had an overall larger reduction in SFCT compared to patients treated with half-fluence PDT (Son et al., 2019). In addition, two studies showed similar results between half-time PDT and half-dose PDT (Liu et al., 2016b; Shiode et al., 2015). Furthermore, a previous study by Liu et al. found that patients with cCSC who were treated with half-dose/full-fluence PDT had a higher rate of complete SRF resolution compared to patients treated with half-dose/half-fluence PDT (Liu et al., 2014). Several studies also compared various dosages of verteporfin in an attempt to determine the lowest effective treatment dosage for CSC. Specifically, one-third dosage was compared to half-dose PDT

and was found to be inferior primarily in terms of SRF recurrence rate and improvement in BCVA (Dang et al., 2014; Park et al., 2021; Pichai et al., 2021; Uetani et al., 2012; Zhao et al., 2015).

2.3.1.2. PDT in acute CSC

Although spontaneous SRF resolution is relatively common in aCSC, treatment of aCSC with PDT has been studied in a few RCTs (Table 2), with complete SRF resolution reported in 74-100% of cases (Chan et al., 2008; Hu et al., 2021; Kim et al., 2014; Missotten et al., 2021; Zhao et al., 2015). First, Chan et al. performed a prospective, placebo-controlled, RCT involving 63 patients with aCSC; 43 patients were randomized to receive ICGA-guided half-dose PDT, and 21 patients received placebo (Chan et al., 2008). The authors found that complete SRF resolution at 12 months was achieved in 95% of patients who received half-dose PDT compared to only 58% of patients who received placebo, a significant difference between groups. Moreover, mean BCVA at 12 months was significantly better in the treatment group compared to the placebo group (Chan et al., 2008). These results suggest that half-dose PDT may be a viable treatment option for aCSC, despite the high probability of achieving spontaneous SRF resolution if left untreated (Mohabati et al., 2020a). In contrast, Missotten and colleagues performed a RCT to assess whether PDT can be safely deferred in aCSC when the leakage point on FA is within 1 optic disc diameter from the fovea (Missotten et al., 2021). This study included 52 patients; half randomized to receive half-fluence PDT and evaluated at 3 months (with subsequent follow-up visits every 3 months), while the other 26 patients were randomized to observation only. At 3 months, BCVA improved faster and metamorphopsia improved significantly in the PDT group compared to the control group, although no statistically significant difference was observed between the two group at 12 months. It should be noted that PDT was performed if any leakage or SRF was observed at the 3-, 6-, or 12-month evaluation visit, regardless of the group, which may have obscured the results at the 12-month follow-up visit, particularly given the relatively low number of patients in each group (Missotten et al., 2021). Some retrospective studies of patients with aCSC have found that PDT can provide faster SRF resolution and a more rapid recovery of retinal sensitivity (Casalino et al., 2016; Hagen et al., 2013), and additionally, a higher BCVA improvement compared to placebo was observed in a RCT (Chan et al., 2008).

Two RCTs compared PDT settings for the treatment of aCSC. The first study, by Zhao and colleagues, found that half-dose PDT (i.e., 50% of the standard dose) was more effective at inducing complete SRF resolution and achieving better visual outcome than 30% of the standard dose (Zhao et al., 2015). More recently, Hu et al. studied 51 eyes in 45 patients with aCSC and found that SRF resolved completely in 57% and 91% of eyes 1 month and 3 months, respectively, in patients who received ICGA-guided half-dose PDT, compared to 70% and 96%, respectively in patients who

received OCT-A–guided half-dose PDT (Hu et al., 2021). Thus, OCT-A–guided PDT was noninferior to ICGA-guided PDT with respect to complete SRF resolution at 3 months.

In addition to the aforementioned RCTs in aCSC, which had relatively small sample sizes, a number of non-randomized retrospective studies regarding the use of PDT in the treatment of aCSC have also been performed. For example, Kim et al. compared outcome in 11 patients who received FA-guided half-dose PDT and 10 patients who received placebo (Kim et al., 2014). The authors found complete SRF resolution in 80%, 100%, and 90% at 1, 3, and 12 months, respectively, in the PDT groups, compared to only 18%, 27%, and 64% of patients, respectively, in the placebo group. Additionally, the long-term change in BCVA and the rate of complete SRF resolution were not significantly different between patients who received half-dose PDT compared to patients who did not receive any treatment (with 90% and 64% of patients, respectively, achieving complete SRF resolution at 12 months).

Treatment with low-fluence PDT may also lower the risk of SRF recurrence in aCSC. For example, Ozkaya et al. performed a case-control study involving 77 patients and found that 51% of untreated patients had a recurrence of SRF, compared to only 25% of patients treated with low-fluence PDT (Ozkaya et al., 2016). In addition, Mohabati and colleagues performed a large retrospective study including 295 eyes with typical aCSC (which the authors defined as documented presence of SRF on OCT, only one area of focal leakage on FA, and limited RPE alterations—including PEDs—of an area smaller than 1 optic disc diameter) and found that SRF recurrence occurred in 24% of untreated eyes, compared to only 4% of eyes that received early treatment, the majority of which received half-dose PDT (Mohabati et al., 2020a).

In conclusion, even though patients with aCSC have a relatively high likelihood of spontaneous SRF resolution, half-dose PDT seems to be a suitable treatment option for aCSC, as it may lead to more rapid SRF resolution and more rapid recovery of retinal sensitivity, and may therefore be indicated for some patients, particularly those who require a rapid improvement in vision, for example for professional reasons (Fig. 4 A-J) (Lu et al., 2016; Ober et al., 2005; Tsai and Hsieh, 2014). On the other hand, simply observing patients with aCSC for several months does not seem to significantly affect long-term visual outcome (Kim et al., 2014; Missotten et al., 2021).

2.3.1.3. PDT in chronic CSC

PDT as a treatment for cCSC was first reported by Yannuzzi and colleagues in 2003, in which the authors reported complete SRF resolution in 12 out of 20 eyes (60%) at 6 weeks following PDT using standard (“full dose”) settings (Yannuzzi et al., 2003). In the same year, Cardillo Piccolino et al. reported complete SRF resolution in 12 out of 16 eyes (75%) at 1 month following full-dose PDT (Cardillo Piccolino et al., 2003). Although short-term and long-term adverse effects of full-setting

PDT in cCSC are extremely rare (Vasconcelos et al., 2013), several subsequent studies used a reduced verteporfin dose for the treatment of cCSC, providing evidence of a better safety profile and similar efficacy compared to full-dose PDT (Chen et al., 2008; Nicholson et al., 2013), half-fluence PDT, and half-time PDT (Liu et al., 2016b; Shiode et al., 2015).

In recent years, several RCTs have added to the body of evidence supporting the use of half-dose PDT as a first-line treatment for cCSC. First, the investigator-initiated PLACE trial by Van Dijk et al. and the first large RCT in cCSC compared ICGA-guided half-dose PDT to high-density subthreshold micropulse laser treatment (HSML) in 179 patients with cCSC (van Dijk et al., 2018b). At 6-8 weeks following treatment, SRF had resolved in 51% of the half-dose PDT–treated patients, compared to only 14% of the HSML-treated patients ($p<0.001$). A similar improvement in the PDT group was also observed at 7-8 months, with 67% and 29% of patients, respectively, having resolved SRF ($p<0.001$). In addition, 6-8 weeks after treatment, the PDT-treated patients had a significantly higher increase in BCVA compared to the HSML-treated patients (+4.60 ETDRS letters vs. +1.39 ETDRS letters, respectively, $p=0.011$), although this difference was no longer significant 7-8 months after treatment (+6.78 and +4.48 ETDRS letters, respectively, $p=0.099$). Retinal sensitivity on microperimetry has also been shown to be an important measure of successful treatment, as BCVA can be relatively preserved in patients with CSC, despite the presence of SRF (Karakus et al., 2013). In the PLACE trial, the increase in mean retinal sensitivity was significantly higher at both 6-8 weeks ($p=0.046$) and 7-8 months ($p=0.008$) in the half-dose PDT group than in the HSML group (van Dijk et al., 2018b).

The patients with cCSC who presented with persistent SRF at their final visit during the PLACE trial despite receiving the primary treatment (half-dose PDT or HSML) were subsequently invited to participated in a follow-up crossover study—the REPLACE trial—and received the crossover treatment (i.e., those who received half-dose PDT in the PLACE trial received HSML in the REPLACE trial, and vice versa) (van Rijssen et al., 2020b). In this crossover study, 82% of the 32 patients who received half-dose PDT as the crossover treatment had complete SRF resolution 6-8 weeks after treatment, compared to 0% of the 10 patients who received HSML patients; moreover, increase in mean retinal sensitivity was significantly larger in the PDT group compared to the HSML group ($p<0.001$) (van Rijssen et al., 2020b). In a second follow-up study of the PLACE trial, 44 patients with cCSC (specifically, 29 and 15 patients, respectively, who had received half-dose PDT and HSML, respectively, in the PLACE trial) who had achieved complete SRF resolution at the end of the PLACE trial were evaluated one year later (van Rijssen et al., 2021b). These authors found that 93% of the patients in the half-dose PDT group still had complete SRF remission at their 1-year visit, compared to only 53% of patients in the HSML group ($p=0.006$), indicating that patients with cCSC who receive ICGA-guided HSML are less likely to achieve long-term SRF remission. The authors suggested that this finding may be due to the fact that unlike PDT, HSML does not target the choroid, the tissue primarily affected in CSC. In addition, patients who were successfully treated with half-

dose PDT in the PLACE trial (defined as complete SRF resolution at the final visit) were also less likely to have SRF recurrence at 20 months compared to patients successfully treated with HSML. However, the authors found no difference in functional outcome between these two treatment groups at the long-term follow-up (van Rijssen et al., 2021b).

A subsequent investigator-initiated RCT in the Netherlands called the SPECTRA trial compared treatment with half-dose PDT to treatment with oral eplerenone (25 mg/day for 1 week, then increased to 50 mg/day if the patient's potassium levels were sufficient) in 107 patients with cCSC (van Rijssen et al., 2022). Three months after baseline, significantly more patients in the half-dose PDT group had complete SRF resolution compared to the eplerenone-treated patients (78% vs. 17%, respectively, $p<0.001$), as well as a significantly larger increase in retinal sensitivity ($p=0.041$) (van Rijssen et al., 2022). Similar to the findings reported in the REPLACE trial, the patients in the SPECTRA trial who had persistent SRF 3 months after primary treatment then received the crossover treatment and were evaluated 3 months later in the follow-up SPECS trial (Feenstra et al., 2022c). Three months after crossover treatment, 32 out of 37 (87%) of patients who received half-dose PDT as the crossover treatment still had complete SRF resolution, compared to only 2 out of 9 patients (22%) who received eplerenone as the crossover treatment ($p=0.030$). Furthermore, the patients who were enrolled in the SPECTRA trial were re-evaluated 12 months after baseline, with complete SRF resolution observed in 90% and 88% of patients who were initially received half-dose PDT or eplerenone, respectively. This small difference between treatment groups should be taken with a grain of salt, however, as 83% of the 42 patients who initially received eplerenone subsequently received half-dose PDT in the SPECS crossover trial due to persistent SRF on OCT, compared to only 22% of the patients initially received half-dose PDT followed by eplerenone treatment in the SPECS trial. Nevertheless, the 12-month improvement in BCVA was significantly larger in the patients who initially received primary half-dose PDT compared to the patients who initially received eplerenone ($p=0.030$), despite no significant difference in macular retinal or foveal sensitivity on microperimetry measured between these two groups at the 1-year follow-up visit (Feenstra et al., 2022b).

Lastly, Park and colleagues performed a RCT involving 43 eyes in 42 patients with cCSC in order to investigate the effect of using different fluence rates (50%, 40%, and 30%) with PDT (Park et al., 2021). The authors found that a 50%-fluence was the most effective, with the lowest recurrence rate (0%) and the highest rate of complete SRF resolution (100%) at 12 months, compared to recurrence rates of 46% and 25% in the 40%-fluence and 30%-fluence groups, respectively, and complete SRF resolution rates of 60% and 81%, respectively. In addition, 12 months after PDT, mean BCVA improved significantly in both the 50%-fluence ($p=0.003$) and 40%-fluence ($p=0.005$) groups relative to baseline, but not in the 30%-fluence group (Park et al., 2021).

Several retrospective studies using PDT for the treatment of cCSC have also been performed, with complete SRF resolution rates ranging from 21% to 100% (see Table 2). For example, in a large

retrospective study of 204 patients with cCSC Fujita et al. found complete SRF resolution in 89% of patients 12 months after half-dose PDT (Fujita et al., 2015). Moreover, the long-term benefits of half-dose PDT are generally favorable, as two studies found complete SRF resolution rates of 81% and 91% after a mean follow-up of 50 and 19 months, respectively (Dhirani et al., 2017; Haga et al., 2017). Reduced-setting PDT also has favorable long-term outcome with respect to BCVA, with an average increase of 5 ETDRS letters measured 7-8 months after reducing-setting PDT in the PLACE trial (van Dijk et al., 2018b), and a mean increase of 9 ETDRS letters in patients 4 years after receiving full-setting PDT (Silva et al., 2013).

Recurrence of SRF after prior complete resolution was also examined after ICGA-guided half-dose PDT for cCSC. Dhirani and colleagues found that SRF recurred in 13% of patients after a mean follow-up of 19 months, Haga et al. found a recurrence rate of 18% after a mean follow-up of 50 months, while Son et al. found a recurrence rate of 0% after a mean follow-up of 40 months (Dhirani et al., 2017; Haga et al., 2017; Son et al., 2019). In a retrospective study of 61 patients who underwent half-time PDT, Hayashisa et al. found that patients who underwent FA-guided half-time PDT had a significantly higher rate of recurrence and/or persistent SRF compared to patients who underwent ICGA-guided half-time PDT (Hayashida et al., 2020). This difference in efficacy between FA-guided and ICGA-guided PDT may be explained by the fact that choroidal abnormalities are the underlying cause of CSC; thus, FA-guided PDT may not sufficiently treat CSC, as abnormalities identified on FA are generally more focal than—and secondary to—the underlying choroidal abnormalities (Hayashida et al., 2020; van Rijssen et al., 2021a).

In the treatment of cCSC, half-dose PDT has been associated with a lower recurrence rate compared to PDT using lower doses (Park et al., 2021; Pichai et al., 2021). Moreover, Silva and colleagues found that only 3 out of 46 (4%) eyes with cCSC had persistent SRF 4 years after receiving full-dose PDT (Silva et al., 2013). In addition, the likelihood of SRF recurrence is lower after PDT compared to both HSML and oral eplerenone (Kim et al., 2019a; van Rijssen et al., 2019a). One year after treatment in the PLACE trial, only 7% of patients who received half-dose PDT had a recurrence of SRF, compared to nearly half (47%) of the patients who received HSML (van Rijssen et al., 2021b). In a retrospective study of 75 eyes with unspecified CSC treated with either half-dose PDT or placebo, by Lai and colleagues found that only 20% of eyes in the half-dose PDT group had a recurrence of SRF compared to 53% of eyes in the placebo group at the 3-year follow-up visit (Lai et al., 2015). In a subsequent study, Lai et al. found that compared to patients with unilateral cCSC the recurrence rate after half-dose PDT was higher in patients with bilateral cCSC, possibly indicating more severe and/or extensive disease (Lai et al., 2016).

Several predictors of treatment outcome following PDT for CSC have been reported, including: 1) the presence of posterior cystoid retinal degeneration; 2) absence of an intense hyperfluorescent area on ICGA prior to PDT; 3) poor baseline BCVA; 4) a disruption in the EZ; 5) a diffuse (i.e., not focal)

hyperfluorescent pattern on ICGA; 6) the presence of shallow, irregular PEDs on OCT, which can be suggestive of type 1 MNV; and 7) lower central macular thickness at baseline (Arora et al., 2021c; Cardillo Piccolino et al., 2008; Chung et al., 2018; Fujita et al., 2015; Nicolo et al., 2012; van Rijssen et al., 2018b). Interestingly, a study by Breukink et al. did not find a clear correlation between corticosteroid use and outcome after PDT in patients with cCSC (Breukink et al., 2016a). Importantly, if the disruption in the EZ remains after complete SRF resolution, BCVA can remain poor.

In some cCSC cases, re-treatment with PDT may be required due to persistent SRF. However, in the PLACE trial, only 32% of patients who received a second round of half-dose PDT due to persistent SRF achieved complete SRF resolution at their subsequent follow-up visit (van Dijk et al., 2018b). Importantly, hypofluorescent changes on ICGA may predict a potential lack of response to repeated PDT (Inoue et al., 2010; van Rijssen et al., 2018b). RPE atrophy has been linked to reduced choroidal permeability, which results in hypofluorescence on ICGA (Spaide et al., 1996b), possibly due to progressive quiescence of the choriocapillaris after long-lasting disease and chronic RPE atrophy (Bhutto and Lutty, 2012). If choroidal leakage and congestion are present—which can be seen as multifocal hyperfluorescence on ICGA and multifocal leakage on FA—the patient is more likely to have a favorable response to PDT than if the choriocapillaris is a thinned and quiescent due to chronic damage. Nevertheless, a second PDT treatment may still be effective in some patients with CSC, particularly cases with SRF due to persistent—or recurrent—hyperfluorescent choroidal changes on ICGA in association with focal leakage on FA.

Several studies have also examined PDT for the treatment of PEDs associated with SRF in CSC and found positive results regarding complete PED resolution (Arf et al., 2017; Arif et al., 2018; Feenstra et al., 2021; Goto et al., 2012; Hwang et al., 2018). For example, a retrospective study of 123 patients with macular PED who were treated with either half-dose PDT or HSML in the PLACE trial found that half-dose PDT was significantly better than HSML with respect to reducing the height of macular PEDs in active cCSC (Feenstra et al., 2021). In a retrospective interventional study, 35 eyes in 35 patients with serous subfoveal PED associated with CSC were treated with reduced-fluence PDT (with 6 mg/m^2 verteporfin and 30-36 mJ/cm^2 light intensity); 1 month after treatment, 28 eyes (80%) had complete resolution of the subfoveal PED, and recurrences of subfoveal PEDs were observed 10 months after treatment (Hwang et al., 2018).

In conclusion, a growing body of evidence obtained in recent years support the use of half-dose PDT as the preferred treatment option for cCSC (Fig. 4 K-DD). Nevertheless, a large RCT comparing half-dose PDT to placebo is warranted in order to further demonstrate the efficacy of half-dose PDT.

2.3.1.4. Safety of PDT in CSC

An initial concern regarding the safety of PDT in CSC was the risk of choroidal ischemia and subsequent retinal atrophy, based primarily on previous reports of choroidal ischemia and vision loss in patients with AMD treated—often multiple times—with PDT using standard ("full") settings (Rishi et al., 2011; Wachtlin et al., 2003). However, extrapolating data from AMD to CSC can be difficult given the differences in their etiology and age of onset. In AMD, the choroid is generally reduced at baseline and presents with an altered RPE and often the presence of sub-RPE material such as drusen. This constellation of findings is in stark contrast with CSC and the pachychoroid disease spectrum, which typically present with an abnormally thickened choroid, dilatation and overload of the veins in Haller's layer, and a dysfunctional, hyperpermeable choriocapillaris. In CSC, PDT—applied using either standard or reduced settings—actually reverses the abnormally thickened choroid and reduces choroidal hyperpermeability (Maruko et al., 2010; van Rijssen et al., 2021a; van Rijssen et al., 2019b); in contrast, PDT in both AMD and PCV is aimed at the retinal and/or subretinal neovascularization. This difference likely underlies the findings PDT-induced choroidal ischemia and acute vision loss is extremely rare in CSC cases (Feenstra et al., 2023; Pinto et al., 2022).

Importantly, several large prospective RCTs and many retrospective studies have shown that adverse events are rare following half-dose PDT (Bae et al., 2014; Fujita et al., 2015; Liu et al., 2014; Park et al., 2021; Son et al., 2019; Tseng and Chen, 2015; van Dijk et al., 2018b; van Rijssen et al., 2022; Zhao et al., 2015). Importantly, using higher laser fluence or a higher dosage of verteporfin may increase the risk of adverse events. For example, Schlotzer-Schrehardt and colleagues found that both the risk and severity of adverse effects increased when fluence was 100 J/cm^2, double the standard fluence of 50 J/cm^2 and four times the fluence used in half-fluence PDT, which is often used for the treatment of diseases in the pachychoroid disease spectrum (Schlotzer-Schrehardt et al., 2002). In addition, a meta-analysis comparing full-dose PDT to placebo in patients with MNV due to AMD, a higher prevalence of visual disturbances were reported in the PDT-treated group compared to the placebo group (22-42% versus 16-23%, respectively), including visual field defects and decreased and/or abnormal vision (Azab et al., 2004). In addition, the authors found that 1-5% of the patients treated with full-dose PDT experienced an acute decrease in BCVA (Azab et al., 2004); however, Arnold et al. found that up to 71% of patients with AMD who experience an acute decrease in BCVA improved by at least one line after 3 months (Arnold et al., 2004). On the other hand, a study involving 46 cCSC eyes in 42 cCSC found that full-dose PDT was not associated with either systemic or ocular side effects up to 4 years after treatment (Silva et al., 2013).

Adverse events associated with PDT can include systemic events such as headache, back pain, nausea, dyspnea, dizziness, and syncope (Borodoker et al., 2002; Pece et al., 2006; Schnurrbusch et al., 2005). These adverse events can present after both full-setting and reduced-setting PDT and are related to the

use of verteporfin. Side effects at the site of verteporfin infusion can also occur and can include skin edema, pain, extravasation, and inflammation; however, these side effects are relatively rare, occurring in <1% of cases (van Dijk et al., 2018b; van Rijssen et al., 2022). In addition to systemic side effects related to verteporfin infusion, other—albeit extremely rare—side effects can include a hypersensitive reaction to the infusion (including an anaphylactic reaction with convulsions) and temporary renal artery stenosis, which can manifest as severe back pain during verteporfin infusion and typically resolves after stopping the infusion. Pregnancy, porphyria, and poor liver function are contraindications for PDT (Raizada and Naik, 2022).

Although uncommon, ophthalmic adverse events have also been reported to occur following half-dose PDT. One such short-term adverse event, PDT-induced acute exudative maculopathy (PAEM), was recently identified. PAEM is defined as subretinal exudation occurring within days following PDT and can present either with or without an acute decrease in vision (Fernandez-Vigo et al., 2023; Fernandez-Vigo et al., 2022; Honda et al., 2022; Mammo and Forooghian, 2017; Manayath et al., 2020; van Dijk et al., 2018a). Thus, although difficult to confirm transient choroidal ischemia and inflammation, which can result in excessive vascular permeability, may underlie this adverse event (Fernandez-Vigo et al., 2022; van Dijk et al., 2018a). Recently, Fernandez-Vigo and colleagues performed a prospective observational case series involving 92 eyes in 75 patients with CSC in which SRF was present for at least 3 months and who underwent half-fluence PDT during which the treatment spot was centered on the fovea (Fernandez-Vigo et al., 2022). The authors found that PAEM occurred 3 days after PDT in 28 out of 92 eyes (30.4%), although they found no significant difference in the rate of complete SRF resolution at 3 months between patients who developed PAEM and patients who did not. Interestingly, on average the patients who developed PAEM had a worse baseline BCVA compared to patients who did not develop PAEM (72 vs. 77 ETDRS letters, respectively, p=0.048). The authors performed a long term-follow up study, which included 64 eyes of 64 of the aforementioned patients who had a follow-up of at least 2 years (Fernandez-Vigo et al., 2023). At 2 years, there were no differences in BCVA change between patients with and without PAEM, with an increase of 4.2 and 7.1 ETDRS letters, respectively (p=0.055). In addition, a small prospective study by Van Dijk et al. involving 14 eyes in 13 patients with cCSC who underwent half-dose PDT found worsening of visual complaints in 5 patients (38%) 1 week after treatment, with no significant difference in central foveal thickness, SRF height, choroidal thickness, or retinal sensitivity on microperimetry between in the 5 patients who experienced worsening of visual symptoms and the 8 patients who did not (van Dijk et al., 2018a). In summary, although acute post-PDT PAEM is not particularly uncommon, it appears to have a self-limiting course and favorable outcome (Fernandez-Vigo et al., 2022; Mammo and Forooghian, 2017; Manayath et al., 2020; van Dijk et al., 2018a).

Previously, Yannuzzi suggested that baseline presence of subretinal fibrin in the serous detachment in CSC—which may be associated with lower baseline BCVA and poorer outcome if left untreated

(Liang et al., 2021; Rezai and Eliott, 2004; Schatz et al., 1995; Shinojima et al., 2010)—may be a risk factor for vision loss following PDT (Yannuzzi, 2010). However, Liang et al. conducted a relatively large case series in patients with unspecified CSC who received half-dose PDT and found no difference in BCVA improvement or SRF resolution between patients who presented with subretinal fibrin and patients who presented without subretinal fibrin; moreover 91.7% of patients with subretinal fibrin at baseline achieved complete SRF resolution and good visual outcome, with no ocular adverse events reported (Liang et al., 2021).

Long-term ophthalmic adverse events following PDT are relatively rare, but can include atrophy of the RPE, atrophy of the choroid, and development of a MNV; however, all of these events can also occur naturally, making a causal link between these complications and PDT difficult to establish (Feenstra et al., 2022b; Peiretti et al., 2018; Son et al., 2019; van Rijssen et al., 2021b; Vasconcelos et al., 2013). Despite the favorable safety profile of PDT for the treatment of CSC, a retrospective study by Lim and colleagues revealed RPE atrophy and an acute severe decrease in vision in 4% and 1.5% of eyes, respectively, in patients with unspecified CSC who received either half-fluence PDT (128 patients) or full-fluence PDT (130 patients) (Lim et al., 2014). On the other hand, we recently studied 57 patients with cCSC from the PLACE and SPECTRA RCTs who were treated with fovea-involving half-dose PDT, but found no signs of RPE atrophy on multimodal imaging 2 years after treatment (Feenstra et al., 2023). Another recent study by Pinto et al. found that similar efficacy and safety following foveal and extrafoveal application of half-dose PDT in 70 eyes in 47 patients with cCSC (Pinto et al., 2022).

In a recent retrospective interventional study involving 559 eyes in 520 patients with CSC who received PDT, Hwang et al. found that 1.25% of eyes developed MNV within 3 months (Hwang et al., 2021); specifically, 6 out of 138 eyes (4.35%) with a flat irregular PED developed MNV, compared to only 1 out of 421 eyes (0.24%) without a flat irregular PED ($p<0.001$). In addition, a retrospective interventional case series that included 204 eyes with cCSC treated with half-dose PDT found no ocular or systemic side effects other than a polypoidal lesion in one patient 8 months after treatment (Fujita et al., 2015). However, it should be noted that the development of PCV can reflect the natural course of CSC, as the presence of MNV is relatively common, with reported rates as high as 36% among patients with cCSC prior to receiving treatment (Peiretti et al., 2015; Serra et al., 2022; Zhou et al., 2022b); thus, the development of MNV may not necessarily be attributed solely to PDT (Fujita et al., 2015). In addition, a retrospective study by Shin et al. found no difference in MNV development between patients with CSC were treated with a focal laser (1 out of 33 eyes developed MNV after 12 months) compared to patients treated with half-dose PDT (1 out of 29 eyes developed MNV after 81 months) (Shin et al., 2011). Lastly, Wu and colleagues studied 70 eyes in 61 patients with cCSC who previously received half-dose PDT and found that as many as 32 patients had MNV visible on OCT-A with a mean interval of 40 months between half-dose PDT and follow-up OCT-A imaging. The

authors also found that the patients who developed MNV were generally older, received PDT with a larger spot size, and had thinner SFCT at baseline compared to the patients who did not develop MNV (Wu and Chen, 2019).

Whether patients with CSC who receive multiple PDT treatments have a higher risk of adverse effects is currently unknown. However, a recent retrospective study by Pauleikhoff and colleagues involving 55 patients with cCSC who underwent a bilateral half-dose PDT found that 73 of the 110 eyes (66%) had complete SRF remission 5 months after treatment, with no adverse events reported (Pauleikhoff et al., 2023).

Taken together, these studies provide extensive evidence suggesting that PDT is a safe and effective treatment option for CSC.

2.3.2. Conventional laser photocoagulation

Focal continuous-wave thermal laser photocoagulation (also known as continuous wave laser, focal laser, and conventional laser) was traditionally used to treat extrafoveal leakage in CSC (Leaver and Williams, 1979); this treatment was typically performed using a diode laser or argon laser, but has also been performed using a krypton laser or xenon laser (Nicholson et al., 2013; Novak et al., 1987). With conventional laser photocoagulation, the focal leakage points on FA are targeted. Importantly, conventional laser photocoagulation is suitable only for treating extrafoveal leakage points, as adverse events such as scotoma, vision loss, reduced contrast sensitivity, and/or MNV can occur at the treated area due to damage to the neuroretina-RPE-Bruch's membrane at the treatment site (Chhablani et al., 2016; Daruich et al., 2015; Ficker et al., 1988; Gemenetzi et al., 2010).

Although conventional laser photocoagulation can reduce the duration of SRF, studies found no significant difference in BCVA between treated patients and untreated patients with unspecified CSC (Robertson, 1986; Robertson and Ilstrup, 1983). In another study from the pre-OCT era, Burumcek et al. found that the time to reach complete SRF resolution was shorter in eyes with persistent CSC that were treated with conventional laser photocoagulation on the focal leakage point compared to untreated eyes (Burumcek et al., 1997). Moreover, the prevalence of SRF recurrence after a mean follow-up period of 4.8 years was significantly lower in the conventional laser photocoagulation–treated group, (0 out of 29 eyes) compared to 7 out of 16 eyes in the untreated group (Burumcek et al., 1997). A RCT conducted by Verma and colleagues found that using a diode laser yielded a superior outcome compared to using an argon laser in terms of BCVA improvement measured in 30 patients with unspecified CSC (Verma et al., 2004).

Navigated conventional laser photocoagulation has been suggested to provide a safe and effective continuous-wave laser modality for treating CSC (Chhablani et al., 2014; Muller et al., 2018). Using navigated conventional laser photocoagulation, the information obtained from fundus photography

and FA imaging is integrated in order to identify the area to be treated. Using this integrated information, a computer then performs automated photocoagulation using a 532-nm laser (Kozak et al., 2011). Several studies applied navigated conventional laser photocoagulation to the focal leakage point on FA and yield complete SRF resolution rates of 75-100% among patients with CSC, although BCVA outcome varied (Chhablani et al., 2014; Muller et al., 2018; Shin et al., 2020). A recent retrospective chart review of 62 patients with CSC who were treated with conventional laser photocoagulation and 29 patients who were treated with full-dose PDT found that the patients treated with conventional laser photocoagulation took longer to reach SRF resolution compared to the patients treated with full-dose PDT (1.8 vs. 1.2 months, respectively, p=0.005); however, at their 3-year follow-up they found no difference in BCVA between the two treatment groups (Shin et al., 2020). In addition, the recurrence rate in the PDT-treated group was only 10%, compared to 30% in the conventional laser photocoagulation–treated group. In a recent retrospective study, Yamada-Okahara and found a significantly higher rate of complete SRF resolution 3 months after treatment in 42 patients who received half-fluence PDT compared to 7 patients who received conventional laser photocoagulation (81% vs. 29%, respectively) (Yamada-Okahara et al., 2023). A long-term prospective RCT that compared conventional laser photocoagulation to no treatment found no difference in recurrence rate or BCVA in 69 patients with undefined CSC measured 6-12 years after treatment (Ficker et al., 1988). Zhou and colleagues randomized 110 patients with aCSC to received treatment with either 577-nm HSML or conventional laser photocoagulation (Zhou et al., 2021). Three months after treatment, 73% of the patients in the HSML group had complete SRF resolution, compared to 89% of the patients treated with a conventional laser photocoagulation (p=0.029); at 6 months, the complete SRF rate was similar between the two (86% vs. 93%, respectively, p=0.221). Moreover, 6 months after treatment, the authors found no significant difference in BCVA (Zhou et al., 2021). Another RCT compared HSML to conventional laser photocoagulation in 88 patients with unspecified CSC and found that complete SRF resolution rates of 64% and 82%, respectively, 12 weeks after treatment; however, this difference was not significant (p=0.056) (Sun et al., 2020). In addition, at 12 weeks the gain in BCVA was similar between the HSML and conventional laser photocoagulation groups, with average gains of 6 and 7 ETDRS letters, respectively (the p-value for non-inferiority was 0.0026). In contrast, Piasecka et al. found a lower rate of complete SRF resolution rate at 12 months in patients treated with HSML compared to patients treated with conventional laser photocoagulation (74% and 88%, respectively); however, the increase in BCVA was larger in the HSML group compared to the conventional laser photocoagulation group (Piasecka et al., 2020). Lastly, Maruko et al. found that in contrast to PDT treatment, treating CSC with conventional laser photocoagulation did not change SFCT (Maruko et al., 2010). This finding may be explained by the underlying choroidal abnormalities in CSC, which may not be treated as effectively using conventional laser photocoagulation.

In conclusion, when PDT—the preferred treatment option due to its favorable outcome—is not available or not indicated, conventional laser photocoagulation can be considered for treating extramacular focal leakage points (van Dijk et al., 2022b).

2.3.3. Subthreshold micropulse laser

With subthreshold micropulse laser treatment, the aim is to selectively target the RPE without causing visible tissue damage. Micropulse laser treatment was first used as a treatment for macular edema in patients with diabetic retinopathy or retinal vein occlusion (Friberg and Karatza, 1997; Moorman and Hamilton, 1999). This treatment was later proposed for CSC (Chen et al., 2008; Lanzetta et al., 2008).

Although micropulse laser treatment has been used for over two decades, its mechanism of action remains poorly understood. During treatment, photons are delivered to the retina in a train of brief (100-500 μs duration) laser pulses, thus allowing heat to dissipate between pulses. Using this approach, the temperature of the tissue stays below the threshold at which cellular proteins start to denature, and laser-induced burns are avoided. Chromophores present in the RPE (primarily melanin) absorb the photons' energy, which is dissipated as heat (Sivaprasad et al., 2010). When applied at sublethal levels, this treatment is believed to increase the expression of heat shock proteins; because this increase in expression is believed to restore cellular function in the RPE, it can be particularly relevant for treating chorioretinal diseases such as CSC (Sramek et al., 2011).

With high-threshold subthreshold micropulse laser (HSML), the diffusion of heat to surrounding tissues is minimized, thereby preventing tissue coagulation and scarring. To treat CSC using HSML, the laser spots are typically targeted to the hyperfluorescent abnormalities seen on ICGA (although some groups target the focal leakage points visible on FA). The laser spots are packed closely together in a dense pattern, with adjacent, non-overlapping spots focused on the designated treatment area (Fig. 5) (Luttrull, 2016; Malik et al., 2015; van Dijk et al., 2018b).

A wide combination of micropulse laser strategies and laser types have been studied and recommended in interventional studies in CSC (summarized in Table 3), which complicates comparisons between studies and makes reproducing the putative benefits difficult. Laser settings that can be adjusted include the wavelength, duty cycle (the percentage of time that the laser is actively emitting laser light), power (i.e., laser intensity), treatment spot size, and pulse duration (defined as the interval between each pulse cycle). To date, 810-nm, 577-nm, 532-nm, and 527-nm wavelengths have been studied. With respect to duty cycle, studies have used values ranging from 5% to 15% (Breukink et al., 2016b; Maruko et al., 2017). Power levels ranging from 90 mW to 1800 mW have been used (Wood et al., 2017), with spot size ranging from 100 μm to 200 μm (Ntomoka et al., 2018; Roca et al., 2018). Lastly, pulse duration ranged from 100 ms to 300 ms (Ambiya et al., 2016; Malik et al., 2015). To achieve a duty cycle of 5-15% with a 200-ms pulse divided into 100 micropulses, the

laser must be on for 100-300 µm during each 2 ms micropulse (Abd Elhamid, 2015). In theory, if spot size is decreased, the energy can be delivered to the retina with higher precision. The combination of the aforementioned settings determines the "dose" of energy delivered to the retina. This dose should be titrated until a therapeutic effect is reached without causing damage to the neuroretina or RPE. For example, in the PLACE trial the laser power was reduced in 300-mW increments if any retinal discoloration was visible after a test spot was targeted outside the macula (van Dijk et al., 2018b). In a recent study, by Ivanova and colleagues used a computer simulation of tissue heating and protein denaturation to determine the micropulse modes that would result in selective damage to the RPE using various laser power settings (Ivanova et al., 2022). Their simulation suggested that a micropulse duration of 50-100 µs, a duty cycle of 2.4-4.8%, a 10-ms pulse envelope (i.e., 5 micropulses), and a spot diameter of 100 µm would provide efficiency and selectivity values >67% and would correspond to the optimal therapeutic window for delivering targeted RPE damage at a given power; increasing micropulse duration, the number of micropulses, and/or the duty cycle would likely decrease the targeted effect on the RPE and cause higher damage to adjacent tissues (Ivanova et al., 2022). To date, no large, prospective RCTs designed to compare various micropulse laser protocols in CSC have been reported. The high degree of variability in the settings used in micropulse laser treatment make it extremely difficult to compare results between different studies using HSML in CSC, and this is further complicated by the fact that these studies included additional variability with respect to clinical parameters such as inclusion criteria, exclusion criteria, and outcome measures.

To date, only a few large RCTs tested the use of subthreshold micropulse laser to treat cCSC. The PLACE trial was the first large RCT to study the use of ICGA-guided HSML in cCSC (van Dijk et al., 2018b). In this RCT, 90 patients were assigned to receive HSML treatment, and 89 patients were assigned to receive half-dose PDT. For this study, an 810-nm diode laser was directed a minimum distance of 500 µm from the foveal center, with a duty cycle of 5%, a frequency of 500 Hz, and a duration of 200 ms. An average of 187 spots at a mean power of 1739 mW were applied, with a total of 99 patients requiring a second treatment. At 6-8 weeks following treatment, SRF had resolved in 51.2% of the patients who received half-dose PDT, compared to only 13.8% of patients who received HSML (p<0.001). At the final evaluation visit 7-8 months after the baseline visit, 67.2% of the patients in the half-dose PDT group had complete SRF resolution, compared to only 28.8% of patients in the HSML group. The patients who had not achieved complete SRF resolution by the end of the PLACE trial were also invited to receive the crossover treatment in a follow-up study, the REPLACE trial (van Rijssen et al., 2020b). Among 9 patients in the original PDT group who had persistent SRF and received HSML as the crossover treatment, 67% had complete SRF resolution 1 year after treatment (p=0.109). In addition, the patients who had complete SRF resolution at their final visit in the PLACE trial were also evaluated 1 year after completion of the PLACE trial, showing that 93% of

patients treated with half-dose PDT had complete SRF resolution, significantly higher than the HSML-treated patients (53%, p=0.006) (van Rijssen et al., 2021b).

Ho and colleagues recently conducted a RCT to compare 577-nm subthreshold micropulse laser to half-dose PDT in 33 patients with cCSC (Ho et al., 2021). In this relatively small study, 18 patients were randomly assigned to receive 577-nm subthreshold micropulse laser treatment, while the remaining 15 patients were assigned to received half-dose PDT. Three months after treatment, an absence of SRF at the fovea was seen in 50% of patients in the micropulse laser group, compared to 87% of patients treated with half-dose PDT (p=0.030). Lastly, Sun et al. compared FA-guided 577-nm HSML with 577-nm threshold conventional laser in a RCT involving 44 patients with unspecified CSC per treatment group (Castro-Correia et al., 1992; Sun et al., 2019; Wang et al., 2002). Twelve weeks after treatment, 64% of patients who received HSML had complete SRF resolution, which was lower—albeit not statistically significant (p=0.056)—than in the conventional laser group (64%); in addition, the authors found no significant difference in BCVA gain between the two groups.

With respect to aCSC, one RCT was conducted to study micropulse laser treatment (Zhou et al., 2021). In this study, 55 patients with aCSC received 577-nm micropulse laser treatment, while another 55 patients were treated with conventional laser photocoagulation. Three months after treatment, 73% of patients in the subthreshold micropulse laser group had complete SRF resolution, significantly lower than in the conventional laser group (89%, p=0.029). Patients who still had SRF at 3 months were re-treated using the same treatment; 6 months later, 86% of the patients treated with subthreshold micropulse laser had complete SRF resolution, which was similar to the conventional laser group (93%, p=0.221). The authors also found significant difference between the treatment groups with respect to the change in BCVA, central foveal thickness, or central retinal thickness.

Given the results of the four aforementioned trials, micropulse laser treatment appears to be inferior to both half-dose PDT and conventional laser photocoagulation with respect to SRF resolution. Importantly, conventional laser photocoagulation can only be performed in cases in which the origin of fluid leakage is extrafoveal and preferably extramacular.

Some authors have suggested that subthreshold micropulse laser treatment may be more effective at treating focal leakage than diffuse leakage in cCSC (Chen et al., 2008). For example, a subgroup analysis of the PLACE trial data consisting of 79 HSML-treated who presented with either focal or diffuse leakage on FA found that 41% and 21% of patients, respectively, had complete SRF resolution 7-8 months after HSML treatment (van Rijssen et al., 2019a). Importantly, however, irrespective of the leakage pattern half-dose PDT led to a significantly higher percentage of patients with cCSC having complete SRF resolution compared to HSML, with complete SRF resolution in 75% versus 41%, respectively, of patients with focal leakage and 57% versus 21%, respectively, of patients with diffuse leakage (van Rijssen et al., 2019a).

In addition to RCTs, several retrospective studies and case series regarding the use of micropulse laser treatment in CSC have been reported (see Table 3). Together, these studies show that overall, 24-100% of patients with cCSC had complete SRF resolution after treatment with HSML. In a retrospective study by Chhablani and colleagues, 51% of patients with "CSC" (including patients with acute, chronic, persistent, and/or recurrent CSC) who were treated with 577-nm subthreshold micropulse laser had complete SRF resolution after a mean follow-up of 10 months (Chhablani et al., 2021). Moreover, a prospective interventional trial by Schworm and colleagues found that 54% of patients with cCSC had complete SRF resolution 12 months after receiving at least one round of 577-nm subthreshold micropulse laser treatment, although it is important to note that 77% and 14% of these patients were previously treated with eplerenone and half-dose PDT, respectively (Schworm et al., 2021). Lastly, Scholz et al. studied 38 patients with cCSC who were treated with 577-nm micropulse laser and found that 24% of these patients had complete SRF resolution after a mean follow-up of 5 months (Scholz et al., 2015). In addition to complete SRF resolution and BCVA, several other outcomes have also been evaluated following HSML treatment, including retinal thickness (Amoroso et al., 2021; Koss et al., 2012; Kretz et al., 2015; Park et al., 2017), choroidal thickness (Amoroso et al., 2021; Arsan et al., 2018), retinal sensitivity on microperimetry (Abd Elhamid, 2015; Schworm et al., 2021), ERG response (Goel et al., 2021), and adverse events (Roca et al., 2018).

Relatively few side effects have been reported following subthreshold micropulse laser treatment (Chhablani et al., 2021; Roca et al., 2018; Zhou et al., 2021). In the PLACE RCT, one patient with cCSC treated with HSML developed a vision-threatening adverse event in which BCVA decreased by more than 30 ETDRS letters; this decline in BCVA was considered to have been caused by an increase in SRF, independent of the HSML treatment, and was therefore deemed not to be treatment-related (van Dijk et al., 2018b). In the above-mentioned RCT by Sun and colleagues, the authors reported that no laser-induced scarring was detected, but mild RPE depigmentation was observed in 12% of patients with unspecified CSC who were treated with subthreshold micropulse laser, although this could have been associated with the normal clinical course in CSC (Castro-Correia et al., 1992; Sun et al., 2019; Wang et al., 2002). However, a prospective observational study which included 149 eyes of 146 cCSC patients who received HSML found that 7 out of 149 eyes developed hyperplasia of the RPE after treatment, which occurred subfoveally in 6 out of 7 cases (Enriquez-Fuentes et al., 2023). In this group, the mean visual acuity loss was 14.1 ETDRS letters. Among the patients who were treated with a fluence of ≥ 45 J/cm^2, 23% developed hyperplasia of the RPE.

To summarize, although subthreshold micropulse laser appear to be safe for use in treating CSC, recent RCTs have shown that it is inferior to both half-dose PDT and conventional laser in terms of achieving complete SRF resolution. This finding may be explained by the fact that micropulse laser treatment does not target the choroid, the tissue in which the primary and most extensive underlying

abnormalities are present in CSC (Ho et al., 2021; van Rijssen et al., 2021a). Nevertheless, a large number of other studies, including retrospective studies, suggest some degree of improvement in patients who received subthreshold micropulse laser treatment; however, many studies are complicated by the fact that CSC has a waxing and waning nature and the tendency to improve spontaneously, even in cCSC (Lotery et al., 2020; van Rijssen et al., 2020a). Recently, a meta-analysis by Van Dijk et al. found that treating cCSC with subthreshold micropulse laser does not have a significantly lower odds ratio regarding the presence of SRF after a follow-up of approximately 2 months compared to untreated patients, with an odds ratio of 13.5 (95% CI: 0.9 to 207.6; p=0.0620) (van Dijk et al., 2022b). Therefore, we conclude that subthreshold micropulse laser is not the treatment of choice for CSC.

Table 3.

Overview of studies using micropulse laser treatment for central serous chorioretinopathy.

Study	CSC subtype	Study design	Mean age (years)	Laser	Settings	Number of eyes	Follow-up (months)	Complete resolution of subretinal fluid (%) at final follow-up	Reported parameters and outcomes
(Arora et al., 2018)	aCSC	Randomized controlled trial	35	810-nm diode laser	Spot size: 125 µm, duration: 200 ms, pulse envelopes: 100×300-µs micropulses, duty cycle: 15% Guidance system: not specified Number of spots: not specified	34 eyes (34 patients)	6	Not reported	Mean LogMAR BCVA improved from 0.59 to 0.03, mean contrast testing chart improved +0.51, mean SRF height decreased 239 µm.
(Behnia et al., 2013)	aCSC	Randomized controlled trial	39	532-nm laser	Spot size: 100 µm, duration: 500 ms, power: 80 mW, then reduced by 20% until no visible burns occurred Guidance system: not specified Number of spots: not specified	18 eyes (18 patients)	6	Not reported	Mean LogMAR BCVA improved from 0.26 to 0.12 (p=0.052).
(Gawęcki et al., 2019)	aCSC	Retrospective case series	48	577-nm laser	Spot size: 160 µm, duration: 200 ms, duty cycle: 5%, power: 250 mW Guidance system: OCT (covering whole SRF area) Number of spots: not specified	32 eyes (32 patients)	6	81%	Mean LogMAR BCVA increased from 0.37 at baseline to 0.22 after treatment.
(Goel et al., 2021)	aCSC	Prospective randomized interventional study	39	532-nm subthreshold laser	Spot size: 100 µm, duration: 100-200 ms, duty cycle: not specified, power: increased to produce a mild grey lesion at the level of the outer retina, after which the duration was halved to 100 ms Guidance system: FA-guided	15 eyes (15 patients)	6	Not reported	Mean LogMAR BCVA increased from 0.44 at baseline to 0.02 at 6 months.

					Number of spots: not mentioned				
(Zhou et al., 2019a)	aCSC	Prospective interventional non-randomized comparative case series	41	577-nm laser	Spot size: 100 µm, duration: 200 ms, duty cycle: 5%, power: 50% or 25% of threshold burn (just visible minimal graying reaction on the retina) Guidance system: not specified Number of spots: max 50 in 1 session	54 eyes (54 patients)	3	83% (50% power group), 54% (25% power group)	Mean LogMAR BCVA improved from 0.27 to 0.02 in the 50% power group, and from 0.34 to 0.14 in the 25% power group.
(Zhou et al., 2021)	aCSC	Randomized controlled trial	41	577-nm subthreshold micropulse laser	Spot size: 100 µm, duration: 200 ms, duty cycle: 5%, power: 400-600 mW Guidance system: not specified Number of spots: not specified	55 eyes (55 patients)	3	73%	Mean LogMAR BCVA increased from 0.11 at baseline to 0.03 at 3 months.
(Altınel et al., 2021)	cCSC	Retrospective study	47	577-nm subthreshold micropulse laser	Spot size: 160 µm, duration: 200 ms, duty cycle: 5%, power: 700 mW Guidance system: not specified Number of spots: not specified	39 eyes (39 patients)	12 (mean)	36%	Mean LogMAR BCVA improved from 0.26 to 0.24 at 12 months in the complete SRF remission group, 0.43 to 0.42 in the partial SRF remission group, and 0.53 to 0.44 in the group without SRF remission.
(Arsan et al., 2018)	cCSC	Prospective study	43	577-nm subliminal laser	Spot size: 160 µm, duration: 20 ms, duty cycle: 5%, power: 50% of minimum threshold value for a visible burn Guidance system: FA-guided Number of spots: not specified	39 eyes (39 patients)	12	92%	Median LogMAR BCVA increased from 0.40 to 0.0.

(Ashraf et al., 2018)	cCSC	Prospective nonrandomized interventional case series	38	MC300 photocoagulator (532 nm)	Spot size: 100 µm, duration: 150 ms, wavelength: 80–100 mW, power: 70% of the threshold spot (mean: 60 mW) Guidance system: FA-guided Number of spots: not specified	20 eyes (20 patients)	3-7	75%	Mean BCVA improved from 20/80 to 20/40.
(Breukink et al., 2016b)	cCSC	Interventional prospective case series	48	810-nm diode laser	Spot size: 125 µm, duration: 200 ms, duty cycle: 5%, power: ≤1800 mW Guidance system: ICGA-guided Number of spots: not specified	10 eyes (10 patients)	2–32	10%	Not reported within HSML-treated subgroup.
(van Dijk et al., 2018b)	cCSC	Open-label multicenter randomized controlled clinical trial	49	810-nm micropulse laser	Spot size: 125 µm, duration: 200 ms, duty cycle: 5%, power: 1800 mW ICGA-guided Number of spots: 187 (mean) ± 209	90 eyes (90 patients)	8	29%	Mean ETDRS BCVA improved +1 letter, mean retinal sensitivity increased +2 dB.
(Gawecki et al., 2017)	cCSC	Retrospective study	56	577-nm micropulse laser	Spot size: 160 µm, duration: 200 ms, duty cycle: 5%, power: 250 mW Guidance system: the whole SRF area (on OCT and FA) was covered was targeted Number of spots: not specified	51 eyes (51 patients)	12	71%	Mean LogMAR BCVA improved from 0.39 to 0.56.
(Ho et al., 2021)	cCSC	Double-blind randomized controlled trial	53	577-nmsubthreshold micropulse laser	Spot size: 200 µm, duration: 200 ms, duty cycle: 5%, power: 340-400 mW Guidance system: not specified Number of spots not specified	18 eyes (18 patients)	6	50% (at 3 months)	The LogMAR BCVA improved from 0.31 at baseline to 0.11 at 6 months.
(Işık et al., 2020)	cCSC	Retrospective study	42	577-nm subthreshold micropulse laser	Spot size: 160 µm duration: 200 ms, duty cycle: 5%, power: 200-400 mW Guidance system: FA-guided	58 eyes (58 patients)	6-37	12% (1 month), 67% (3 months), 67% (last follow-up)	Median LogMAR BCVA improved from 0.22 at baseline

					Number of spots: not specified				to 0.0 at 3 months and 0.0 at final follow-up.
(Kim et al., 2015c)	cCSC	Retrospective case series	44	577-nm subthreshold micropulse laser	Spot size: 100 µm duration: 20 ms, duty cycle: 15%, power: 250–350 mW Guidance system: FA-guided Number of spots: 198-3960	10 eyes (10 patients)	6–24 (8 mean)	Not reported	Mean LogMAR BCVA improved from 0.21 at baseline to 0.055 at final visit.
(Kim et al., 2019b)	cCSC	Retrospective interventional study	45	577-nm subthreshold micropulse laser	Spot size: 100 µm, duration: 20 ms, duty cycle: 15%, power: 200-400 mW, increased by 100 mW depending on the SRF resolution Guidance system: over the area of SRF leakage (not specified OCT/FA/ICGA) Number of spots: not specified	27 eyes (27 patients)	44 months (mean)	82%	Mean LogMAR BCVA improved from 0.26 at baseline to 0.08 at 3-year follow-up. (Only included 22/27 patients who had complete SRF resolution during follow-up).
(Kretz et al., 2015)	cCSC	Randomized controlled trial	47	810-nm diode Laser	Spot size: 75–125 µm, duration: 300 ms, duty cycle: 15%, power: 1000 mW Guidance system: FA-guided Number of spots: not specified	20 eyes (20 patients)	4	80%	Mean ETDRS BCVA improved from 87 to 94 letters.
(Malik et al., 2015)	cCSC	Retrospective, interventional case series	Not specified	810-nm subthreshold micropulse laser	Spot size: not specified, duration: 200–300 ms, duty cycle: 5%, power: 750-1000 mW Guidance system: FA-guided Number of spots: 96-657	11 eyes (10 patients)	2–12	Not reported	Mean ETDRS BCVA improved from 39 at baseline to 46 letters after treatment.
(Ntomoka et al., 2018)	cCSC	Retrospective study	49	577-nm microsecond subthreshold laser	Spot size:100 µm, duration: 200 ms, duty cycle: 5%, power: 30% of threshold for a visible burn Guidance system: FA-guided	22 eyes (20 patients)	6	59%	Mean LogMAR BCVA improved from 0.5 to 0.3.

					Number of spots: not specified				
(Ozmert et al., 2016)	cCSC	Retrospective comparative case series	45	577-nm subthreshold micropulse laser	Spot size: 160 µm, duration: 200 ms, duty cycle: 5%, power: 50% of threshold for a visible burn Guidance system: OCT-guided Number of spots: not specified	15 eyes (patients)	≥12	80%	Mean ETDRS BCVA improved from 67 at baseline to 75 letters at 12 months.
(Piasecka et al., 2020)	cCSC	Retrospective observational study	49	532-nm micropulse laser	Spot size: 200 µm, duration: 150 ms, duty cycle: 5%, power: 700-900 mW Guidance system: 3-4 laser spots were applied to the leakage site defined in FA Number of spots: not specified	35 eyes (35 patients)	12	74%	Mean decimal BCVA improved from 0.53 at baseline to 0.89 at final visit.
(Ricci et al., 2009)	cCSC	Interventional prospective non-comparative case series	39	810-nm micropulse laser	Spot size: 112.5 µm, duration: 200 ms, duty cycle: 10%, power: 500mW Guidance system: ICGA-guided Number of spots: not specified	7 eyes (7 patients)	12	71%	Mean BCVA improved 0.19 LogMAR.
(van Rijssen et al., 2020b)	cCSC	Prospective randomized controlled crossover trial	51	810-nm diode laser	Spot size: 125 µm, duration: 200 ms, duty cycle: 5%, power: 1800 mW, frequency: 500 Hz Guidance system: ICGA-guided Number of spots: not specified	10 eyes (10 patients)	12 (after crossover treatment)	0% After crossover treatment with HSML after failure of primary treatment with half-dose PDT, none of the patients had SRF resolution.	Mean ETDRS BCVA decreased from 81 letters at baseline to 80 at 12 months. Mean retinal sensitivity on microperimetry decreased from 24 dB at baseline to 23 at 12 months. Mean NEI-VFQ-25 remained 84 points at 12 months.

(Roca et al., 2018)	cCSC	Multicenter, retrospective comparative study	44	577-nm micropulse laser	Spot size: 100–200 µm, duration: 200 ms, duty cycle: 5%, power: 320–660mW Guidance system: FA- and/or ICGA-guided Number of spots: not specified	92 eyes (92 patients)	12	92%	Mean LogMAR BCVA improved from 0.41 to 0.21.
(Roisman et al., 2013)	cCSC	Prospective randomized double-blind sham controlled pilot trial	40	810-nm micropulse diode laser	Spot size: 125 µm, duration: 300 ms, duty cycle: 15%, power: 1.2 x minimum threshold value for a visible burn Guidance system: not specified Number of spots: 457 (range 299-674)	10 eyes (10 patients)	12	90%	Mean ETDRS BCVA improved from 35 to 50 letters.
(Scholz et al., 2015)	cCSC	Retrospective study	51	577-nm micropulse laser	Spot size: 160 µm, duration: 200 ms, duty cycle: 5%, power: titration started at 700 mW, treatment with 50% of threshold for a visible burn Guidance system: FA- and ICGA-guided Number of spots: not specified	38 eyes (38 patients)	5	24%	Mean LogMAR BCVA improvement was 0.06.
(Scholz et al., 2016)	cCSC	Retrospective study	49	577-nm micropulse laser	Spot size: 160 µm, duration: 200 ms, duty cycle: 5%, power: titration started at 700 mW, treatment with 50% of threshold for a visible burn Guidance system: FA- and ICGA-guided Number of spots: not specified	42 eyes (42 patients)	1.5	36%	Treatment response (decrease in central retinal thickness of 20 µm) after HSML in 79% of the patients.
(Schworm et al., 2021)	cCSC (77% previously treated with eplerenone and 14% with half-dose PDT)	Prospective interventional trial	48	577-nm laser	Spot size: 200 µm, pulse duration: 15 ms, duty cycle: not specified, energy: 100-200 mW Guidance system: not specified Number of spots: 400-420	42 eyes (39 patients)	6	43% (6 months), 54% (12 months) 14% treated once, 19% twice, 17% 3 times, and 45% 4 times.	Mean ETDRS BCVA improved from 80 letters at baseline to 85 letters at 6 months. The average retinal sensitivity on microperimetry changed from

									19 dB to 21 dB at 6 months.
(Sousa et al., 2020)	cCSC	Retrospective cohort study	52	532-nm high-density subthreshold micropulse laser	Spot size: 160 µm, duration: 200 ms, duty cycle: 5%, power: increased upward to the minimum threshold burn on micropulse mode outside vascular area at the posterior pole and afterwards reduced to 50% Guidance system: covering the fluid seen on SD-OCT and/or the main leakage point in FA Number of spots: not specified	26 eyes (22 patients)	3	50%	Median LogMAR BCVA remained at 0.20 12 weeks after baseline.
(Vignesh et al., 2020)	cCSC	Retrospective study	31	577-nm subthreshold micropulse laser	Spot size: 100 µm, duration: 200 ms, duty cycle: 5%, power: 50% of the power used to produce a barely visible burn at a test spot nasal to disc Guidance system: ICGA-guided Number of spots: not specified	28 eyes (27 patients)	8 (mean)	43%	Mean LogMAR BCVA increased from 0.42 at baseline to 0.28 at final visit.
(Yadav et al., 2015)	cCSC	Retrospective study	49	577-nm laser	Spot size: 200 µm, duration: 200 ms, duty cycle: 10%, power: 50% of threshold for a visible burn Guidance system: ICGA-guided Number of spots: 264 (mean; range 74-443)	15 eyes (13 patients	2 (mean)	40%	Median BCVA improved from 20/40 to 20/30. The average decrease in SRF height was 79%.
(Abd Elhamid, 2015)	Non-resolving CSC	Prospective interventional non-comparative clinical study	36	577-nm subthreshold micropulse laser	Spot size: 200 µm, duration: 200 ms, duty cycle: 10%, power: 3x the power needed for threshold burn in continuous wave mode (before switching to micropulse mode). Mean power: 318±70.63 mW. Guidance system: FA-guided Number of spots: 248±85	15 eyes (patients)	6	Not reported	Mean Snellen BCVA improved +0.18, mean Pellin-Robson contrast sensitivity improved +0.25.
(Ambiya et al., 2016)	Non-resolving CSC	Prospective study	38	577-nm microsecond laser	Spot size: 100 µm, duration: 100 ms, duty cycle: 5%, power: 30% of threshold power	10 eyes (10 patients)	6	60%	Mean ETDRS BCVA improved 3

					Guidance system: FA-guided Number of spots: not specified				letters, mean low contrast BCVA improved -0.13 LogMAR, mean retinal sensitivity improved 2 dB.
(Ambiya and Kumar, 2020)	Non-resolving CSC with subfoveal leaks (excluding cCSC)	Retrospective study	37	532-nm subthreshold micropulse laser	Spot size: 100 µm, duration: 200 ms, duty cycle: 5%, power 140-240 mW. A 5x5 grid of confluent spots was applied over the area of focal leak, using the same settings with just 20% of the threshold power Guidance system: FA-guided Number of spots: not specified	23 eyes (21 patients)	6	70%	Mean ETDRS BCVA improved from 66 letters at baseline to 80 letters at 6 months. Contrast sensitivity improved from 0.75 to 1.30 at 6 months.
(Amoroso et al., 2021)	Persistent/ cCSC	Retrospective observational case series	52	5% navigated micropulse laser	Spot size: 100 µm, duration: 100 ms, duty cycle: 5%, power: 30% of the threshold laser burn power Guidance system: FA and/or ICGA-guided Number of spots: 436	39 eyes (36 patients)	3	Not reported	Mean LogMAR BCVA increased from 0.39 at baseline to 0.20 at 6 months. Mean SFCT decreased from 434 µm at baseline to 396 µm at 6 months. Mean PED height decreased from 64 µm at baseline to 30 µm at 6 months.
(Beger et al., 2012)	CSC	Comparative, controlled prospective study	51	810-nm micropulse	Spot size: 125 µm, duration: 200 ms, duty cycle: 15%, power: mean 1313 mW Guidance system: FA-guided Number of spots: 71	16 eyes (patients)	10	87.5%	Mean ETDRS BCVA improved 6 letters.

(Chhablani et al., 2021)	Acute, chronic, persistent, and recurrent CSC (26% previously treated with MR antagonists)	Retrospective study	50	577-nm subthreshold microsecond pulsing laser	Spot size: 100-200 µm, duration: 100-200 ms, duty cycle: 2.5%-15%, power: 19-881 (mean 206) mJ/mm^2 27% underwent more than a single microsecond laser session Guidance system: not specified Number of spots: 78-438	101 eyes (86 patients)	10 (mean)	51%	Mean LogMAR BCVA improved from 0.35 at baseline to 0.27 at final follow-up.
(Chen et al., 2008)	Idiopathic CSC	Prospective non-comparative interventional case series	44	810-nm micropulse diode laser	Spot size: 125 µm, duration: 200 ms, 100 pulses of 300 us over 2 ms, duty cycle: 15%, power: adjusted upward to power needed for threshold burn in continuous wave mode and a duration of 200 ms, after which the apparatus was changed to micropulse mode with a duty cycle of 15% Guidance system: FA-guided Number of spots: not specified	26 eyes (25 patients)	8	50%	BCVA improved ≥3 lines in 58%.
(Gupta et al., 2009)	aCSC and cCSC	Retrospective case series	46	810-nm diode laser	Spot size: 125 µm, duration: 200 ms, duty cycle: 15%, power: 20% of threshold burn Guidance system: FA-guided Number of spots: not specified	5 eyes (5 patients)	6-24	80%	BCVA improved in 3 patients, but remained stable in 2 patients.
(Koss et al., 2012)	CSC	Comparative, controlled prospective study	51	810-nm diode laser	Spot size: 125 µm, duration: 200 ms, duty cycle: 15%, power: 2x threshold power in continuous wave mode with a duration of 200 ms was determined (after switching to micropulse laser mode) Guidance system: FA-guided Number of spots: not specified	52 eyes (52 patients	10	87%	Mean BCVA changed from 16/16 to 2/16.

(Lanzetta et al., 2008)	CSC	Prospective study	47	810-nm micropulse diode laser	Spot size: 200 µm, duration: 200 ms, duty cycle: 15%, power: 1000–2000 mW Guidance system: FA-guided Number of spots: 215 (range, 90–400)	24 eyes (22 patients)	3-36	75% (improved/ resolved)	Median BCVA was 6/9.6 before treatment, and 6/7.5 at the end of follow-up.
(Lavinsky and Palanker, 2015)	CSC	Prospective nonrandomized interventional case series	57	577-nm PASCAL laser	Spot size: 250 µm, duration: adjusted as needed, pulses: 15 ms, power: 90–150mW (30% of threshold burn) Guidance system: covering both the thickened and non-thickened retina in the posterior pole, as determined by the OCT and by increased autofluorescence Number of spots: 532	16 eyes (15 patients)	6	75%	Mean ETDRS BCVA improved 12 letters.
(Luttrull, 2016)	CSC	Retrospective study	44	810-nm subthreshold micropulse laser	Spot size: 200 µm, duration: 150 ms, duty cycle: 5%, power: 1400 mW Guidance system: FA-guided Number of spots: 290-1431	11 eyes (11 patients)	1-45	100%	-
(Prasuhn et al., 2021)	CSC with persistent SRF for at least 3 months	Prospective observational study	54	577-nm subthreshold micropulse laser	Spot size: 200 µm, duration 200 ms, duty cycle: 10%, power: 40-50% of visibility threshold of the leakage points observed in FA Guidance system: around the leakage points observed in FA Number of spots: not specified	27 eyes (27 patients) 17 fellow eyes (as control group)	1	Not reported	Mean LogMAR BCVA increased from 0.4 at baseline to 0.3 after 4 weeks.
(Maruko et al., 2017)	CSC	Retrospective study	47	577-nm micropulse laser	Spot size: 200 µm, duration: 200 ms, duty cycle: 15%, power: 140–200 mW Guidance system: not specified Number of spots: not specified	14 eyes (14 patients)	2	64%	Mean Snellen BCVA improved 0.02, mean SFCT decreased 10 µm.

(Sun et al., 2019)	CSC, not specified	Prospective randomized double-masked clinical trial	44	577-nm high-density micropulse laser	Spot size: 160 µm, duration 200 ms, duty cycle: 5%, power: 50% threshold tested Guidance system: FA-guided Number of spots: 150-200	44 eyes (44 patients)	3	64%	Mean ETDRS BCVA improved from 77 letters to 83 letters 12 weeks after baseline.
(Uzlu et al., 2021)	Chronic or chronic recurrent CSC	Retrospective study	49	577-nm subthreshold micropulse laser	Spot size: 100 µm, duration: 200 ms, duty cycle: 5%, power: 160-200 mW Mean of 284 spots Guidance system: FA-guided Number of spots: 284 ± 190	20 eyes (19 patients)	6	Not reported. Complete SRF resolution was not achieved in any of the cases with a disease duration of 24 months or longer. Complete SRF resolution was achieved in all cases with a disease duration of 9 months or less.	Mean LogMAR BCVA improved from 0.24 at baseline to 0.18 at 6 months after treatment.

aCSC, acute central serous chorioretinopathy; BCVA, best-corrected visual acuity; cCSC, chronic central serous chorioretinopathy; CRT, central retinal thickness; CSC, central serous chorioretinopathy; ETDRS, Early Treatment of Diabetic Retinopathy Study; FA, fluorescein angiography; HSML, high-density subthreshold micropulse laser; LogMAR, logarithm of the minimal angle of resolution; Nd:YLF, neodymium-doped yttrium lithium fluoride NEI-VFQ-25, National Eye Institute Visual Functioning Questionnaire 25-item version; OCT, optical coherence tomography; PASCAL, patterned scanning laser; PDT, photodynamic therapy; PED, retinal pigment epithelial detachment; SFCT, subfoveal choroidal thickness; SRF, subretinal fluid.

2.3.4. Transpupillary thermotherapy

Transpupillary thermotherapy (TTT) was first used in the field of ophthalmology to treat choroidal melanoma (Oosterhuis et al., 1995). The aim of TTT is to induce a mild increase in temperature specifically in the target area (for example, to 45-60°C after 1 minute in the case of choroidal melanoma) (Journee-de Korver et al., 1992). This increase in local temperature (known as ocular hyperthermia) activates a cascade of reactions that presumably involve the production of heat shock proteins, molecular chaperones that help repair damaged RPE cells and may also lead to choroidal vascular thrombosis (Desmettre et al., 2001). Several techniques have been developed to induce ocular hyperthermia, including the use of localized current fields (Liggett et al., 1990), microwave radiation (Lagendijk, 1982), ultrasound (Coleman et al., 1986), and magnetic thermoseeds (Mieler et al., 1989). The mechanism by which TTT can treat CSC is unclear, but TTT is believed to induce vascular thrombosis and/or apoptosis in endothelial cells, which can then treat the underlying choroidal abnormalities in CSC (Wei and Yang, 2005). To treat CSC, TTT can be induced using an 810-nm pulse diode laser, which requires a shorter treatment duration (30-45 seconds) compared to the treatment of choroidal melanomas, as CSC does not involve active proliferation of the choroid (Hussain et al., 2006).

Several studies—albeit with relatively small numbers (i.e., up to 25 eyes per study)—investigated the use of TTT in CSC (Giudice et al., 2011; Hussain et al., 2006; Kawamura et al., 2012; Manayath et al., 2017; Manayath et al., 2012; Mathur et al., 2009; Russo et al., 2017; Shukla et al., 2008). For example, a prospective non-randomized study by Mathur and colleagues involving 25 patients with cCSC found that 52% of patients had complete SRF resolution 3 months after TTT (Mathur et al., 2009). In addition, Manayath and colleagues performed a prospective study comparing 20 patients with cCSC who received PDT with another 22 patients who declined to undergo PDT and therefore underwent TTT (Manayath et al., 2017). The authors found that difference in BCVA was similar between the TTT and PDT groups both at baseline and 6 months after treatment; moreover, mean foveal thickness decreased significantly in both groups. Interestingly, however, the patients in the TTT group required more treatments and took longer to achieve complete SRF resolution (Manayath et al., 2017).

Notably, side effects such as macular infarction can occur following TTT for AMD, albeit on rare occasions (Benner et al., 2002). Therefore, a large, prospective RCT is needed in order to evaluate the safety and efficacy of TTT for the treatment of CSC.

2.3.5. Selective retina therapy (SRT)

In addition to subthreshold micropulse laser, another approach called selective retina therapy (SRT) has also been suggested as a treatment option for CSC. This treatment modality was first described by

Roider and colleagues, who used a 5-μs argon laser to deliver pulses of 514-nm light at a frequency of 500 Hz (Roider et al., 1999; Roider et al., 1992). SRT is believed to work by causing the formation of microbubbles in RPE cells (Neumann and Brinkmann, 2006; Roider et al., 1999; Seifert et al., 2018). This effect was hypothesized to result in selective destruction of RPE cells with high peak temperatures around the melanosomes, without inducing thermal diffusion into surrounding tissues, thereby theoretically leaving the neurosensory retinal tissues and choroid unharmed (Elsner et al., 2006; Klatt et al., 2011; Park et al., 2017; Roider et al., 1992; Seifert et al., 2022).

To date, three relatively small RCTs have been conducted to assess the feasibility of using SRT as a treatment for CSC. First, Klatt and colleagues performed SRT in 14 patients with aCSC, while an additional 16 patients were randomized to the control (untreated) group (Klatt et al., 2011). The authors used a Q-switched frequency doubled neodymium-doped yttrium lithium fluoride (Nd:YLF) laser with a wavelength of 527 nm, with 30 micropulses delivered at a frequency of 100 Hz, a spot diameter of 200 μm, and a duration of 1.7 μs. Before treatment, approximately 5 test pulses of increasing energy were applied adjacent to the vessel arcades in each patient in order to determine the appropriate pulse energy for treatment, determined as the treatment spots being visible by FA but not visible on funduscopy. During treatment, the laser spots were applied to the focal points of leakage assessed on FA. Three months after treatment, 71% of the patients in the SRT group had complete SRF resolution, which was higher—but not significantly different—than the control group (40%, p=0.081). In another RCT, Oh and colleagues randomized 31 patients with unspecified CSC that presented with clinical symptoms for >3 months to treatment with SRT, and 37 patients to a control (sham) group (Oh et al., 2021). The authors used a Q-switched frequency-doubled Nd:YLF laser set to a frequency of 100 Hz, a spot diameter of 200 μm, and a duration of 1.7 μs. Three months after treatment, the rate of complete SRF resolution on OCT was similar between the SRT group and the controls (55% vs. 35%, respectively, p=0.142). In addition, they found significant difference in the increase in BCVA at 3 months between the groups (p=0.054). In contrast, a mixed model for repeated measures analysis showed that the reduction in SRF occurred earlier in the SRT group than in the control group (p=0.0029) (Oh et al., 2021). The third small RCT was performed by Lee and colleagues, who applied real-time-feedback dosimetry-guided SRT in patients with cCSC. In this approach, real-time-feedback dosimetry with both optoacoustic dosimetry and reflectometry is used to detect in real time the formation of transient microbubbles originating from RPE damage, allowing for individualized laser settings and maximizing the safety of SRT. In this study, 22 patients each were assigned to the SRT and control (untreated) groups (Lee et al., 2021a). The authors used a Nd:YLF with a wavelength of 527-nm set to deliver 15 micropulses at a frequency of 100 Hz, a spot diameter of 200 μm, and a duration of 1.7 μs. In contrast to the two aforementioned studies, the authors found a statistically significant difference in complete SRF resolution rates between the SRT group and the

control group after a relatively short follow-up period of 6 weeks (64% and 24%, respectively, p=0.009).

In addition to the aforementioned RCTs, Framme and colleagues performed a study in which 10 patients with aCSC and 16 patients with chronic-recurrent CSC were treated with SRT (Framme et al., 2015). FA was performed 1 hour after treatment to determine whether the desired effect on RPE damage—defined as fluorescein leakage in the spots being visible on FA, but the lesions are not visible ophthalmoscopically (the so-called angiographic threshold)—had been achieved. In cases in which the laser energy was too low (i.e., an absence of fluorescein leakage in the test spots), those patients were re-treated immediately using an adjusted energy setting. Three months after treatment, 100% of the patients with aCSC had complete SRF resolution on OCT, compared to only 19% of the patients with chronic-recurrent CSC. Moreover, between baseline and the 3-month follow-up visit, BCVA increased from 77 to 85 ETDRS letters in the aCSC group, and from 72 to 73 ETDRS letters in the cCSC group (Framme et al., 2015). It should be noted, however, that the apparent positive treatment effect of SRT in the patients with aCSC in this study may have been overstated, as waxing and waning of SRF is part of the natural course of CSC, particularly in aCSC (Mohabati et al., 2020a). Moreover, it is important to note that this study did not include a control group.

The treatment of CSC with SRT has also been studied in a few retrospective studies, which showed a rather wide range of complete SRF resolution rates from 19% to 100% (Table 4) (Elsner et al., 2006; Framme et al., 2015; Klatt et al., 2011). To date, the largest retrospective study on SRT involving CSC was performed by Kim and colleagues (Kim et al., 2022a), in which 137 eyes in 135 patients with cCSC were treated with SRT covering each of the leakage areas on FA. Six months after treatment, complete SRF resolution was achieved in 91% of patients. In addition, mean BCVA improved significantly from 0.41 LogMAR at baseline to 0.33 LogMAR at 6 months (p<0.001), although it should be noted that this study did not include a control group.

Kyo and colleagues studied 77 patients with unspecified CSC in an attempt to identify predictive factors for complete SRF resolution following treatment with SRT, and found a history of non-smoking and focal leakage type on FA (Kyo et al., 2021). Notably, cases with focal leakage without significant atrophic RPE abnormalities—corresponding to a more acute phenotype—have a high likelihood of spontaneous resolution (Mohabati et al., 2020a). In addition, Kim et al. recently reported that baseline SRF height was a significant predictive factor for the need to undergo re-treatment (Kim et al., 2022a).

With respect to the safety of SRT, this has only been studied in relatively small RCTs and retrospective studies; however, the procedure appears to be safe, as least in the short term (i.e., after a follow-up of 3 months) (Framme et al., 2009; Lee et al., 2021a; Oh et al., 2021; Yasui et al., 2017).

However, more information is needed in order to determine the long-term safety and treatment efficacy of SRT.

In summary, evidence supporting the use of SRT in CSC is still rather limited. Only three relatively small RCTs have been performed to date, two of which did not find a significant difference in SRF resolution between SRT-treated patients and controls. On the other hand, a recent systematic review and meta-analysis by Van Dijk and colleagues found that SRT-treated patients may respond better than controls in terms of complete SRF resolution, although the odds ratio (3.4) was markedly lower than the odds ratio for both half-dose or half-fluence PDT (odds ratio: 20.6) and threshold conventional laser therapy (odds ratio: 36.4) (van Dijk et al., 2022b). However, given the current lack of a large RCT studying the effect of SRT, and given that practical clinical experience with this technology is limited, the treatment outcomes reported in these studies should be interpreted with caution. An addition caveat is that SRT presumably treats only the RPE, and not the choroid, and CSC is believed to be caused primarily by a dysfunctional choroid, with the RPE being affected secondarily (Park et al., 2017).

Table 4.

Overview of studies using selective retina therapy in central serous chorioretinopathy.

Study	CSC subtype	Study design	Mean age (years)	Laser	Settings	Number of eyes	Follow-up (months)	Complete resolution of subretinal fluid (%) at final follow-up	Reported parameters and outcomes
(Kim et al., 2018b)	Idiopathic aCSC	Retrospective study	45 (patients over the age of 55 years were excluded)	R:GEN device with a Q-switched Nd:YLF laser. Wavelength: 527 nm	Spot size: 200 µm, duration: 1.7 µs, frequency: 100 Hz, over maximal 15 micropulses Patients were treated with a mean of 5.4 ± 1.2 laser shots around leakage points. The mean maximal laser energy was 105.0 ± 14.6 µJ (range: 80 to 140 µJ)	16 eyes (16 patients)	3	100%	Mean LogMAR BCVA improved from 0.27 at the time of diagnosis to 0.16 at 3 months after treatment.
(Kang et al., 2016)	cCSC	Retrospective study	49	Nd:YLF laser Wavelength: 527 nm	30 pulses per spot, duration: 1.7 us, pulse repetition: 100 Hz	12 eyes (12 patients)	≤12	75% (at 3 months after treatment)	Mean LogMAR BCVA improved from 0.23 at baseline to 0.14 at 3 months after treatment.
(Kang et al., 2016)	Symptomatic cCSC	Retrospective cohort study	49	SRT Q-switched Nd:YLF laser Wavelength: 527 nm	Spot size: not specified, duration: 1.7 µs, frequency: 100 Hz, over 30 micropulses	12 eyes (12 patients)	3	75%	Mean LogMAR BCVA improved from 0.23 at baseline to 0.14 at 3 months.
(Kim et al., 2022a)	cCSC	Retrospective study	48	Q-switched Nd:YLF 527 nm laser, using a SRT device equipped with RFD Wavelength: not mentioned 48 eyes received re-treatment at 3 months	Spot size: 200 µm, duration: 1.7 µs, frequency: not specified The first shot during micropulse laser treatment had an energy of 50% of that of the 15th micropulse. The energy increased by 3.57% per micropulse	137 eyes (135 patients)	6	91%	Mean LogMAR BCVA improved from 0.41 at baseline to 0.33 at 6 months.

(Lee et al., 2021a)	cCSC	Prospective randomized controlled trial	47 (control group), 44 (SRT group)	SRT laser system with RFD-guidance, Nd:YLF laser Wavelength: 527 nm	Spot size: 200 µm, duration: 1.7 µs, frequency: 100 Hz over 15 micropulses	22 eyes (22 patients in SRT group) 22 eyes (22 patients in control group)	1.5	64% (SRT), 24% (control)	Mean LogMAR BCVA improved from 0.20 at baseline to 0.18 at 6 weeks in the control group, compared to 0.25 and 0.23, respectively, in the SRT group. The mean SFCT increased from 370 at baseline to 373 µm at 6 weeks in the control group, whilst this SFCT changed from 351 at baseline to 348 µm at 6 weeks in the SRT group.
(Park et al., 2017)	cCSC	Retrospective case series	51	SRT laser system with RFD, Nd:YLF-laser Wavelength: 527 nm	Spot size: 200 µm, duration: 1.7 µs, frequency: 100 Hz over 15 micropulses Treatment was applied to the areas of leakage observed on FA. If SRF was observed on OCT at 2 months after treatment, retreatment was performed with the same density of treatment spots. However, if SRF height at 2 months after treatment was decreased more than 90% compared to that of baseline, retreatment was not performed	50 eyes (49 patients)	3	74%	Mean LogMAR BCVA improved from 0.44 at baseline to 0.37 at 3 months.
(Yasui et al., 2017)	cCSC (lasting longer than 3 months)	Prospective case series	47	SRT laser frequency doubled, pulse-stretched Nd:YLF laser Wavelength: 527 nm	Spot size: 200 µm, duration: 1.7 µs, frequency: 100 Hz over 30 micropulses	17 eyes (17 patients)	3	65%	The mean LogMAR BCVA improved from 0.06 at baseline to 0.03 at 3 months. Retinal sensitivity in the central 10° increased from

					Energy: 50–150 µJ/pulse				23 dB at baseline to 27 dB at 3 months.
(Büttner et al., 2021)	Persistent aCSC (symptom duration of 6 months or longer and previous treatment with eplerenone)	Prospective observational study	42	R:GEN laser, a micropulse Nd:YLF laser device Wavelength: 527 nm	Spot size: 200 µm, duration: 1.7 µs, frequency: 100 Hz, over maximal 30 micropulses Aimed at the point of focal leakage determined by FA	17 eyes (16 patients)	3	59%	Mean LogMAR BCVA improved from 0.213 at baseline to 0.12 at 3 months.
(Elsner et al., 2006)	Active CSC, not specified	Retrospective study	42 (median)	Pulsed double-Q-switched Nd:YLF prototype laser Wavelength: 527 nm	Spot size: 200 µm, duration: 1.7 µs, frequency: 100 Hz, over a maximum of 30 micropulses For treatment single pulse energies ranging from 100 to 350 µJ were found reasonable	27 eyes (27 patients)	3	100%	Mean Snellen BCVA improved from 20/40 at baseline to 20/20 after 3 months.
(Framme et al., 2015)	aCSC and cCSC	Non-randomized clinical trial	44 (median, aCSC), 52 (median, cCSC)	Diode laser excited Q-switched Nd:YLF laser Wavelength: 527 nm	Spot size: 200 µm, frequency: 100 Hz, over 30 micropulses, duration: 1.7 µs for 5 patients, for the rest of the patients the energy was reduced to 300 µJ	10 eyes (10 aCSC patients) 16 eyes (16 cCSC patients)	3	100% (aCSC), 19% (cCSC)	Mean ETDRS BCVA increased from 77 to 85 letters at 3 months in aCSC patients. Mean ETDRS BCVA changed from 72 at baseline 73 letters after 3 months in cCSC patients.
(Jeon et al., 2021)	cCSC (previously treated with ≥3 intravitreal consecutive bevacizumab injections)	Retrospective cohort study	56	SRT laser system, a Nd:YLF laser Wavelength: 527 nm	Spot size: 200 µm, duration: 1.7 µs, frequency: 100 Hz, over maximal 15 micropulses	22 eyes (22 patients)	12	82%	Mean LogMAR BCVA improved from 0.49 at baseline to 0.43 at 12 months.
(Klatt et al., 2011)	Symptomatic aCSC (minimum of 3 months of	Prospective randomized controlled trial	44	Q-switched frequency doubled Nd:YLF laser Wavelength: 527 nm	Spot diameter: 200 µm, duration: 1.7 µs, frequency: 100 Hz over 30 micropulses	14 eyes (14 patients in SRT group)	3	71% (SRT group), 40% (control group)	Mean ETDRS BCVA improved from 40 to 53 letters at 3 months in patients treated with SRT, compared to 42 and 48

	reduced BCVA)					16 eyes (16 patients in control group)			letters in the control group, respectively.
(Kyo et al., 2021)	CSC (history of more than 3 months with no sign of improvement of CSC diagnosed on OCT)	Retrospective study	51	Q-switched frequency-doubled Nd:YLF laser Wavelength: 527 nm	Spot size: 200 μm, duration: 1.7 μs, frequency: 100 Hz over 30 micropulses	77 eyes (77 patients)	6	60%	Mean LogMAR BCVA improved from 0.08 at baseline to 0.04 at 6 months. The mean SFCT decreased from 352 μm before SRT, to 330 μm at 6 months.
(Oh et al., 2021)	Idiopathic CSC (symptoms present for a minimum of 3 months)	Randomized clinical trial	45 (SRT group), 46 (sham control group)	R:GEN Q-switched Nd: YLF laser Wavelength: 527 nm	Spot size: 200 μm, duration: 1.7 μs, frequency: 100 Hz Pulse energy of 30 to 350 μJ	31 eyes (31 patients in SRT group) 37 eyes (37 patients in sham control group)	3	55% (SRT), 35% (sham control)	Mean LogMAR BCVA improved from 0.18 at baseline to 0.10 at 3 months in SRT group compared to 0.18 and 0.12, respectively in the control group.
(Yamada-Okahara et al., 2023)	Persistent CSC	Retrospective study	50	Q-switched frequency-doubled Nd:YLF laser Wavelength: 527 nm	Spot size: 200 μm, duration: 1.7 μs, frequency: 100 Hz over 30 micropulses	22 eyes (21 patients)	3	59%	No significant changes in BCVA.

aCSC, acute central serous chorioretinopathy; BCVA, best-corrected visual acuity; cCSC, chronic central serous chorioretinopathy; ETDRS, Early Treatment of Diabetic Retinopathy Study; FA, fluorescein angiography; LogMAR, logarithm of the minimal angle of resolution; Nd:YLF, neodymium-doped yttrium lithium fluoride; OCT, optical coherence tomography; PDT, photodynamic therapy; RDF, real-time feedback-controlled dosimetry; SFCT, subfoveal choroidal thickness; SRF, subretinal fluid; SRT, selective retina therapy.

2.3.6. Intravitreal injections of anti-vascular endothelial growth factor (VEGF) compounds

The first anti-VEGF therapy for use in ophthalmology was approved by the US Food and Drug Administration in 2004 and has been used for the treatment of ocular diseases associated with neovascularization, including neovascular AMD, diabetic retinopathy, and retinal vein occlusions. Intravitreal injections anti-VEGF compounds have also been suggested as a possible treatment for CSC due to their ability to modify vascular permeability, as CSC is believed to originate from the choroidal vasculature (Torres-Soriano et al., 2008). Studies have shown that VEGF inhibitors can have anti-proliferative and anti-hyperpermeability effects on choroidal endothelial cells (Gragoudas et al., 2004; Peters et al., 2007). Moreover, the few clinical studies reported to date found that anti-VEGF inhibits leakage and fibrovascular proliferation, decreases choroidal blood flow, and reduces central choroidal thickness in patients with AMD and diabetic macular edema (Koizumi et al., 2016; Nourinia et al., 2018; Roohipoor et al., 2016). Nevertheless, the use of anti-VEGF injections for the treatment of CSC is off-label, and this should be clearly communicated to the patient, and informed consent should be obtained prior to treatment.

Even though several studies investigated anti-VEGF injections for the treatment of CSC—some of which found promising results in terms of improving BCVA (see Table 5)—, to date no large prospective RCTs have been reported. However, one prospective RCT that included only 30 patients with cCSC found that after 6 months 12 out of 15 eyes treated with a single intravitreal injection of the anti-VEGF monoclonal antibody bevacizumab had complete SRF resolution, compared to 8 out of 15 untreated eyes; moreover, 15 eyes (100%) in the treated group had either stable or improved vision, compared to only 10 eyes (67%) in the control group (Artunay et al., 2010). In addition, Kim and colleagues performed a prospective, randomized comparative study involving 20 patients with aCSC who received intravitreal injections of the anti-VEGF antibody ranibizumab and 20 patients who received no treatment (Kim et al., 2013b). The authors found that the mean interval between baseline and complete SRF resolution was 4 weeks in the ranibizumab group, significantly shorter than in the untreated group (13 weeks, $p<0.001$) (Kim et al., 2013b). In a prospective, noncomparative study involving patients with cCSC, Bae et al. found that 12 weeks after treatment complete SRF resolution was achieved in only 13% of eyes treated with ranibizumab injections, compared to 89% of eyes treated with low-fluence PDT (Bae et al., 2014). Lastly, a prospective pilot study by Pitcher and colleagues found that intravitreal injections of the VEGF inhibitor aflibercept led to complete SRF resolution in 6 out of 12 patients with cCSC (50%), but had no significant effect on BCVA (Pitcher et al., 2015). Two independent meta-analyses failed to confirm the putative beneficial effects of bevacizumab, aflibercept, or ranibizumab for treating aCSC, although one study's results partially suggest that patients with cCSC may benefit from anti-VEGF treatment (Chung et al., 2013; Ji et al., 2017).

Importantly, most of the aforementioned studies did not include OCT-A, as they were conducted before this technique became available. It is therefore unclear whether the SRF that resolved was due to CSC or due to a secondary MNV, given that it can be challenging to identify the presence of MNV based solely on FA and ICGA images without the benefit of OCT-A. One recent study compared the effects of intravitreal bevacizumab injections between 30 eyes with cCSC without MNV and 31 eyes with cCSC with MNV detected on OCT-A at baseline (Song et al., 2021). The authors found that the patients with MNV had a more favorable outcome compared to the patients without MNV; specifically, the patients with MNV had a significant improvement in BCVA 1 month after treatment relative to baseline (from 0.31 to 0.24 LogMAR, $p<0.001$), while the patients without MNV had no significant change in BCVA between baseline and their 1-month follow-up (0.23 vs. 0.26, respectively, $p=0.432$) (Song et al., 2021).

No large prospective RCT has been conducted to investigate effects of anti-VEGF in treating CSC without MNV. Therefore, the evidence to date does not appear to support the use of intravitreal anti-VEGF compounds to treat CSC without MNV. However, intravitreal anti-VEGF injections might be beneficial in patients with CSC who also present with MNV and/or polypoidal choroidal vasculopathy (Fig. 6), as discussed in section 3.2.1. (Chan et al., 2007; Chhablani et al., 2015).

1585 **Table 5.**

1586 Overview of studies that assessed intravitreal injections of anti-VEGF compounds for the treatment of central serous chorioretinopathy.

Study	CSC subtype	Study design	OCT-A	Mean age (years)	Anti-VEGF compound and treatment regimen	Number of eyes	Follow-up (months)	Complete resolution of subretinal fluid (%) at final follow-up	Reported parameters and outcomes
(Aydin, 2013)	aCSC	Prospective comparative study	No	46	Single dose of bevacizumab (2.0 mg)	13 eyes (22 patients)	6	Not reported	Mean BCVA improved from 0.39 to 0.73.
(Jung et al., 2019b)	aCSC	Retrospective comparative study	No	51	Intravitreal injection of aflibercept (2.0 mg)	35 eyes (35 patients)	3	46%	SFCT from 444 to 437 µm. Mean LogMAR BCVA improved from 0.30 to 0.19.
(Kim et al., 2013b)	aCSC	Prospective randomized comparative study	No	43	Single dose of ranibizumab (0.5 mg)	20 eyes (20 patients)	>6	100%	Mean LogMAR BCVA improved from 0.37 to 0.17.
(Park et al., 2014)	aCSC	Retrospective study	No	45	Either bevacizumab (1.25 mg) or ranibizumab (0.5 mg) versus placebo	21 eyes (21 patients in anti-VEGF group)	12	95%	Significantly more patients in the anti-VEGF group (57.1%) had a moderate BCVA improvement (<0.1 LogMAR) compared to the control group (26.7%).
(Tekin et al., 2018)	aCSC	Retrospective comparative study	No	43	Either bevacizumab (1.25 mg) or ranibizumab (0.5 mg)	43 eyes (43 patients)	18 (mean)	100% (near complete resolution)	Mean LogMAR BCVA improved from 0.27 to 0.083 at 12 months in the bevacizumab group, compared to 0.26 and 0.045, respectively, in the ranibizumab group.
(Alishiri et al., 2019)	cCSC	Prospective interventional case series	No	42	First injection bevacizumab (1.25 mg), then bevacizumab (2.5 mg) every 4 weeks until complete SRF resolution	22 eyes (22 patients)	4	27.3% (after 1 month), 45.5% (after 2 months), 18.2% (after 3 months), 4.5% (after 4 months), 96% (after 4 months in total)	Mean LogMAR BCVA improved from 0.70 to 0.17. Contrast sensitivity improved from 13.8 to 17.7 dB.

(Artunay et al., 2010)	cCSC	Prospective randomized controlled trial	No	38	Single dose of bevacizumab (2.5 mg)	15 eyes (15 patients)	6	80%	Mean BCVA in LogMAR improved from 0.32 at baseline to 0.03 at final visit.
(Bae et al., 2011)	cCSC	Prospective non-comparative study	No	43	3 consecutive monthly injections of ranibizumab (0.5 mg)	8 eyes (unknown number of patients)	6	75%	Mean LogMAR BCVA improved from 0.38 at baseline to 0.06 at 6 months.
(Bae et al., 2014)	cCSC	Prospective non-comparative study	No	49	3 consecutive monthly injections of ranibizumab (0.5 mg)	16 eyes (unknown number of patients)	12	13%	Mean LogMAR BCVA improved from 0.36 to 0.17.
(Entezari et al., 2012)	cCSC	Prospective non-comparative study	No	40	1 intravitreal injection of bevacizumab (1.25 mg)	5 eyes (5 patients)	6	100%	Mean LogMAR BCVA improved from 0.60 to 0.29.
(Inoue et al., 2011)	cCSC	Prospective non-comparative study	No	46	1-4 intravitreal injections(s) of bevacizumab (1.25 mg)	5 eyes (5 patients)	12	Not reported	Mean LogMAR BCVA improved from 0.23 to 0.17.
(Pitcher et al., 2015)	cCSC	Prospective, non-comparative study	No	54	1 intravitreal injection of aflibercept (2.0 mg)	12 eyes (12 patients)	6	50%	Mean ETDRS BCVA improved from 62 to 64 ETDRS.
(Lee et al., 2011)	cCSC	Retrospective non-comparative case series	No	47	1-6 intravitreal injection(s) of bevacizumab (1.25 mg)	16 eyes (16 patients)	7 (mean)	56%	Mean LogMAR BCVA improved from 0.32 to 0.18.
(Mao et al., 2019)	cCSC	Retrospective study	No	51	1 conbercept (0.5 mg) intravitreal injection. Afterwards, pro re nata. Additional injections of conbercept were administered as needed if either of the following criteria was present: BCVA loss of ≥0.2 LogMAR or evidence of persistent fluid on OCT for more than a 1 month after the previous injection.	35 eyes (31 patients)	6	77.1%	Mean LogMAR BCVA improved from 0.48 to 0.23 after 6 months.
(Mao et al., 2021)	cCSC	Retrospective comparative study	No	51	Either intravitreal injection with conbercept (0.5 mg) or half-dose PDT. Conbercept injection was repeated based on the following criteria: BCVA loss of ≥0.2 LogMAR and persistence of SRF one	37 eyes (37 patients in the conbercept intravitreal injections group)	6	70%	Mean LogMAR BCVA improved from 0.45 to 0.24 at 6 months. SFCT decreased from 395 to 371 μm.

					month after the last injection.				
(Semeraro et al., 2012)	cCSC	Prospective comparative study	No	35	Intravitreal injection(s) of bevacizumab (1.25 mg), as needed	12 eyes (12 patients)	9	Not reported	Mean ETDRS BCVA improved from 20 to 43 letters.
(Chan et al., 2007)	CSC with no MNV	Prospective non-randomized interventional case series	No	38	3 consecutive monthly injections of bevacizumab (1.25 mg)	15 eyes (15 patients)	6	Not reported	Mean LogMAR BCVA improved from 0.48 to 0.17.
(Chang and Cheng, 2020)	Chronic, atypical, and recurrent CSC	Retrospective study	No	46	Bevacizumab (1.25 mg) injections every 6 weeks until complete SRF resolution	77 eyes (71 patients)	12	68%	Mean LogMAR BCVA improved from 0.28 to 0.21 at 12 months.
(Lim and Kim, 2011)	CSC (> 3 months)	Prospective noncomparative study	No	46	1-2 intravitreal injection(s) of bevacizumab (1.25 mg)	40 eyes (40 patients)	>12	83% (within 3 months)	Mean age in the non-resolution group was significantly younger than in the complete resolution group (41 versus 49 years).
(Kim et al., 2015a)	CSC, not specified	Retrospective non-comparative study	No	48	Multiple intravitreal injections of bevacizumab (1.25 mg)	30 eyes (30 patients)	>6	67%	SFCT increased 3 μm in the non-responders group and decreased 63 μm in the responders group.
(Kim et al., 2015b)	Persistent CSC	Retrospective study	No	49	Intravitreal injection(s) of bevacizumab (1.25 mg), as needed	42 eyes (42 patients)	9 (mean)	60%	Mean BCVA improved from 0.35 to 0.32 LogMAR.
(Koss et al., 2012)	CSC (> 3 months)	Prospective comparative study	No	46	1-3 intravitreal injection(s) of bevacizumab (1.25 mg)	10 eyes (10 patients)	10	Not reported	Mean ETDRS BCVA remained at 44 letters.
(Lim et al., 2010)	CSC (>3 months)	Retrospective non-comparative study	No	42	Intravitreal injection(s) of bevacizumab (1.25 mg), as needed	5 eyes (5 patients)	9	100% (5 out of 5 patients)	Mean BCVA improved from 41 to 53 ETDRS letters at 3 months after treatment.
(Peiretti et al., 2018)	CSC with no MNV	Retrospective study of a consecutive series	No	59	Bevacizumab (1.25 mg), ranibizumab (0.5 mg), or pegaptanib (0.3 mg)	18 eyes (18 patients)	12	Not reported	Mean LogMAR BCVA improved from 0.69 to 0.39.
(Roy et al., 2017)	CSC with MNV	Retrospective case series	No	43	Either bevacizumab (1.25 mg) or ranibizumab (0.5 mg)	10 eyes (9 patients)	28 (mean)	60%	Mean BCVA improved from 0.62 to 0.47 LogMAR.
(Song et al., 2021)	cCSC patients with and without MNV	Retrospective case series	Yes	51 (for the patients without MNV)	Single injection of bevacizumab (1.25 mg)	30 eyes (30 patients without MNV)	1	Not reported	Mean LogMAR BCVA decreased from 0.23 to 0.26.
(Unlu et al., 2016a)	CSC, not specified	Retrospective comparative study	No	46	Intravitreal injection(s) of bevacizumab (1.25 mg), as needed	22 eyes (22 patients)	12 (mean)	100% (near complete resolution)	Mean LogMAR BCVA improved from 0.38 to 0.24.

(Unlu et al., 2016b)	CSC, not specified	Retrospective study	No	46	Intravitreal injection(s) of bevacizumab (1.25 mg), as needed	21 eyes (21 patients)	10 (mean)	76%	Mean LogMAR BCVA improved from 0.49 to 0.19, mean SFCT decreased 22 μm (not significant).
(Kang et al., 2020)	CSC (49% aCSC)	Retrospective study	No	46	Bevacizumab injections every 4 weeks until complete SRF resolution	45 eyes (44 patients)	35 (mean)	89%	Mean LogMAR BCVA improved from 0.2 to 0.1 at final visit.

1587 aCSC, acute central serous chorioretinopathy; BCVA, best-corrected visual acuity; cCSC, chronic central serous chorioretinopathy; MNV, macular neovascularization; ETDRS, Early Treatment of Diabetic Retinopathy Study; FA, fluorescein

1588 angiography; LogMAR, logarithm of the minimal angle of resolution; OCT, optical coherence tomography; PDT, photodynamic therapy; SFCT, subfoveal choroidal thickness; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

2.3.7. Mineralocorticoid receptor antagonists and glucocorticoid receptor antagonists

As discussed above, steroid use is one of the significant external risk factors for developing CSC; thus, activation of MRs and GRs may play a role in the pathogenesis of CSC (Ge et al., 2020). Moreover, GRs are expressed in both the choroid and the retina and may therefore play a role in the pathogenic role CSC (Brinks et al., 2018; Brinks et al., 2022a; Brinks et al., 2021a; Zhao et al., 2010).

Interestingly, increased activation of choroidal MRs was observed in rats following an intravitreal injection of corticosteroids (Zhao et al., 2012), supporting the hypothesis that MR antagonists such as eplerenone and spironolactone might be used to treat CSC (Daruich et al., 2015; Zhao et al., 2012; Zhao et al., 2010). Several studies investigated the putative effects of oral MR antagonists in CSC, with mixed results (Table 6). Importantly, patients taking MR antagonists should be monitored closely for potassium levels and renal function both before and during treatment, as MR antagonists may cause hyperkaliemia and related cardiac arrhythmias; thus, creatinine clearance rate of ≤30 mL/min and/or a serum potassium level ≥5.5 mEq are therefore contraindications for treatment with MR antagonists. Nevertheless, a study by Bousquet and colleagues found that patients with a relatively thick choroid (>515 μm) at baseline may respond better to treatment with MR antagonists compared to patients with a thinner choroid (Bousquet et al., 2019).

1606 **Table 6.**

1607 Overview of studies that assessed the effects of oral mineralocorticoid receptor antagonists in central serous chorioretinopathy.

Study	CSC subtype	Study design	Mean age (years)	Drug(s)	Dosage and duration	Number of eyes	Follow-up (months)	Complete resolution of subretinal fluid (%) at final follow-up	Reported parameters and outcome
(Chai et al., 2016)	aCSC	Prospective randomized comparative study	51	Spironolactone and fenofibrate versus fenofibrate	Combination of 200 mg once daily fenofibrate and 100 mg 3 times daily spironolactone or only 200 mg once daily fenofibrate for 8 weeks	60 eyes (60 patients)	2	67% spironolactone + fenofibrate (vs. 40% in fenofibrate group)	Mean LogMAR BCVA improved from 0.35 to 0.22.
(Sun et al., 2018)	aCSC	Prospective randomized controlled clinical study	43	Spironolactone	40 mg, twice daily for 2 months	18 eyes (18 patients)	2	56%	Mean LogMAR BCVA improved from 0.25 to 0.05.
(Zucchiatti et al., 2018)	aCSC	Charts of consecutive patients	44	Eplerenone	25 mg/day for 1 week; 50 mg/day after 1 week for 12 weeks	15 eyes (15 patients)	3	80%	Mean LogMAR BCVA improved from 0.15 to 0.06.
(Bousquet et al., 2013)	cCSC	Non-randomized pilot study	54	Eplerenone	25 mg/day for 1 week, 50 mg/day after 1 week for 1 or 3 months	13 eyes (13 patients)	3	67%	Mean LogMAR BCVA improved from 0.52 to 0.27.
(Falavarjani et al., 2017)	cCSC	Prospective	40	Spironolactone	25 mg/day for a minimum of 6 weeks	16 eyes (14 patients)	6.4 (mean)	44%	Mean LogMAR BCVA improved from 0.54 to 0.42.

		interventional case series							
(Fraenkel et al., 2021)	cCSC	Retrospective study	53	Eplerenone	25 mg/day for 1 week, then 50 mg/day for 6 weeks-3 months depending on the clinical response	30 eyes (30 patients)	3	67%	Mean LogMAR BCVA improved from 0.2 to 0.09 at 3 months.
(Gergely et al., 2017)	cCSC	Prospective clinical trial	49	Eplerenone	50 mg/day for 3 months	28 eyes (28 patients)	6	32%	Mean ETDRS BCVA improved from 75 at baseline to 78 letters at 6 months.
Ghadiali et al. (2016)	cCSC	Retrospective observational case series	58	Spironolactone versus eplerenone	Eplerenone or spironolactone (50 or 25 mg/day)	23 eyes (14 patients)	6–12	Not reported	No change in SFCT.
(Herold et al., 2014)	cCSC	Interventional uncontrolled prospective case series	46	Spironolactone	25 mg twice daily	20 eyes (18 patients)	3	25%	Mean LogMAR BCVA improved from 0.32 at baseline to 0.20 at final visit.
(Iqbal et al., 2021)	cCSC	Retrospective study	56	Eplerenone	50 mg/day for 30 days	13 eyes (13 patients)	1	Not reported	Mean LogMAR BCVA increased from 0.15 at baseline to 0.18 at 4 weeks.
(Karagiannis et al., 2019)	cCSC (previously treated with PDT)	Prospective uncontrolled open-label study	48	Eplerenone	25 mg/day for 4 weeks and 50 mg/day thereafter (in total 6 months)	17 eyes (17 patients)	12	76%	Mean decimal BCVA improved from 0.31 at baseline to 0.69 at 12 months.

(Lotery et al., 2020)	cCSC	Randomized double-blind parallel-group placebo-controlled trial	47	Eplerenone versus placebo	25 mg/day for 1 week, increasing to 50 mg/day up to 12 months	57 eyes (57 patients in eplerenone group)	12	16%	Mean ETDRS BCVA increased from 77 letters at baseline to 80 letters at 12 months.
(Manayath et al., 2021)	cCSC	Retrospective comparative study	49 (eplerenone)	Eplerenone versus half-fluence PDT	25 mg/ day for 1 week, followed by 50 mg/day after serum electrolyte assessment	18 eyes (18 patients in eplerenone group)	12	70%	Mean LogMAR BCVA improved from 0.46 at baseline to 0.33 at 12 months.
(Moein et al., 2019)	cCSC	Prospective study	56	Eplerenone	50 mg/day for 4 weeks	13 eyes (13 patients)	1	Not mentioned	Mean LogMAR BCVA increased from 0.18 at baseline to 0.15 at 4 weeks.
(Petkovsek et al., 2020)	cCSC	Retrospective study	56	Eplerenone	25 or 50 mg/day	100 eyes (83 patients)	21 (mean)	31% (at 1 year)	Mean LogMAR BCVA remained 0.26 at 1 year after baseline.
(Rahimy et al., 2018)	cCSC	Prospective randomized double-blind placebo-controlled study	50	Eplerenone	25 mg/day for 1 week, 50 mg/day after 1 week	15 eyes (10 patients)	2	33%	Mean LogMAR BCVA improved from 0.39 to 0.33.
(Rajesh et al., 2018)	cCSC	Prospective non-randomized study	46	Eplerenone	50 mg/day for 1 month, 25 mg/day for 2 months	22 eyes (11 patients)	6	63%	Mean LogMAR BCVA improved from 0.27 to 0.19.

(van Rijssen et al., 2022)	cCSC	Randomized controlled trial	48 (eplerenone)	Eplerenone versus half-dose PDT	25 mg/day for 1 week, then 50 mg/day for up to 3 months depending on potassium levels	54 eyes (54 patients in eplerenone group)	3	17%	Mean ETDRS BCVA improved from 81 letters at baseline to 83 letters at 3 months. NEI-VFQ25 improved from 79 at baseline to 84 points at 3 months, and retinal sensitivity on microperimetry improved from 23 to 24 dB.
(Sacconi et al., 2018)	cCSC	Interventional open-label non-randomized clinical study	45	Eplerenone	25 mg/day for 1 week, 50 mg/day after 1 week, max. 13 weeks	29 eyes (27 patients)	4.8	58%	Mean LogMAR BCVA improved from 0.20 to 0.10 at the end of treatment, mean SFCT decreased 21 μm.
(Schwartz et al., 2017)	cCSC	Prospective double-blind randomized placebo-controlled study	51	Eplerenone	25 mg/day for 1 week, 50 mg/day after 1 week	13 eyes (unknown number of patients)	Up to 6	23% (after 3 months)	Mean LogMAR BCVA improved from 0.50 to 0.48 LogMAR.
Singh et al. (2015)	cCSC	Retrospective consecutive case series	57	Eplerenone	25 or 50 mg/day for a maximum of 300 days	17 eyes (13 patients)	6 (mean)	35%	Mean LogMAR BCVA improved from 0.43 at baseline to 0.29 at final follow-up.

Zola et al., 2018	cCSC	Retrospective study	53	Eplerenone versus spironolactone	25 or 50 mg/day, mean 21 months (range: 10–24 months)	16 eyes (16 patients)	24	81%	Mean LogMAR BCVA improved from 0.14 at baseline to 0.07 at 24 months.
(Vignesh et al., 2020)	cCSC	Retrospective comparative study	31	Eplerenone versus subthreshold micropulse yellow laser therapy	25 mg/day for 1 month, then 50 mg/day for 2 months	20 eyes (19 patients in eplerenone group)	4.5 (median, eplerenone group)	20%	Mean LogMAR BCVA improved from 0.66 at baseline to 0.71 at final visit in the eplerenone group.
(Borrelli et al., 2019)	aCSC and cCSC	Retrospective cohort study	44	Eplerenone	25 mg/day for 1 week followed by 50 mg/day for 4 weeks, and continued for another 7 weeks depending of the presence of SRF after 5 weeks	50 eyes (50 patients)	12	72%	Mean LogMAR BCVA improved from 0.20 at baseline to 0.10 at 12-months.
Bousquet et al. (2015)	Non-resolving CSC	Randomized controlled crossover study	47	Spironolactone and placebo versus placebo and spironolactone	50 mg/day for 30 days	15 eyes (15 patients)	2	50%	Mean ETDRS BCVA increased from 74 to 77 letters. SFCT decreased 29 μm.
Cakir et al. (2016)	Atrophic/ non-resolving CSC	Retrospective uncontrolled open-label cohort study	56	Eplerenone	25 mg/day for 1 week, 50 mg/day after 1 week	24 eyes (24 patients)	21–364 days	29%	Mean LogMAR BCVA improved from 0.35 to 0.30.
Chin et al. (2015)	Recalcitrant CSC	Retrospective consecutive	58	Eplerenone versus spironolactone versus eplerenone followed by spironolactone	25 or 50 mg twice daily for 1-8.5 months	23 eyes (23 patients)	15	Not reported	Median Snellen BCVA remained at 20/30 at final follow-up in the eplerenone only

		observational case series							group and remained at 20/50 in patients treated with eplerenone followed by spironolactone and decreased from 20/30 to 20/40 at final follow-up in the spironolactone only group.
Daruich et al. (2016)	Non-resolving CSC	Retrospective case series of consecutive patient	53	Eplerenone versus spironolactone	25 mg/day for 1 week, 50 mg/day after 1 week	54 eyes (42 patients)	6	50%	Mean LogMAR BCVA improved from 0.28 at baseline to 0.23 at 6 months.
Herold et al. (2017)	Non-resolving CSC	Interventional uncontrolled open-label prospective clinical trial	47	Spironolactone	25 mg twice daily for 3 months	21 eyes (20 patients)	12	Not reported	Mean LogMAR BCVA improved from 0.25 to 0.17.
(Kapoor and Wagner, 2016)	Unspecified	Retrospective chart review	56 (eplerenone), 59 (spironolactone)	Spironolactone	50 mg/day	32 eyes (32 patients)	3-10	58% (at 3 months)	Mean LogMAR BCVA improved from 0.42 at baseline to 0.31 at 3 months in the spironolactone group, and improved from 0.55 to 0.32 in the eplerenone group.

Kim et al. (2018a)	Steroid induced CSC	Retrospective review	49	Spironolactone	50 mg/day for a mean duration of 2.6 months	17 eyes (15 patients)	17 (mean)	82%	Mean LogMAR BCVA improved from 0.28 to 0.15.
Kim et al. (2019)	Non-resolving CSC	Retrospective, interventional, comparative study	49	Spironolactone	50 mg/day	26 eyes (26 patients)	15 (mean)	69%	Mean LogMAR BCVA improved from 0.39 to 0.2.
Lee et al. (2019)	Non-resolving CSC	Retrospective study	53	Spironolactone	50 mg/day	18 eyes (18 patients)	Up to 6	39%	Mean LogMAR BCVA improved from 0.32 to 0.24.
Pichi et al. (2017)	Persistent CSC	Prospective placebo-controlled trial	51	Eplerenone versus spironolactone	25 mg/day for 1 week, then increase to 50 mg/day, with crossover	60 eyes (60 patients)	4	Not reported	Spironolactone and eplerenone showed a mean reduction in choroidal thickness of 17 and 15 μm, respectively.
Rubsam et al. (2017)	aCSC/cCSC	Interventional controlled and retrospective cohort study	44	Acetazolamide followed by eplerenone or spironolactone	100 mg/day spironolactone or 50 mg/day eplerenone	20 patients (unknown number of patients)	3	Not reported	Mean change in SRF volume was -1.07 mm^3.
(Sinawat et al., 2020)	Persistent CSC (presence of SRF > 3months)	Retrospective comparative study	46	Spironolactone versus conservative treatment.	25 mg twice daily	21 eyes (21 patients in spironolactone group)	6	57%	Mean LogMAR BCVA improved from 0.47 at baseline to 0.38 at 6 months.
(Venkatesh et al., 2020)	Unilateral aCSC	Prospective study	40	Eplerenone versus observation	50 mg/ day for 1 month, then continued until complete SRF resolution	29 eyes (29 patients)	3	62%	At 3 months, all patients in both the eplerenone-treated group as well as the

									observation group had an improvement of visual acuity to 6/6 at 3 months.

aCSC, acute central serous chorioretinopathy; BCVA, best-corrected visual acuity; cCSC; chronic central serous chorioretinopathy; dB, decibel; ETDRS, Early Treatment of Diabetic Retinopathy Study; FA, fluorescein angiography; LogMAR, logarithm of the minimal angle of resolution; MR, mineralocorticoid receptor; NEI-VFQ-25, National Eye Institute Visual Functioning Questionnaire 25-item version; OCT, optical coherence tomography; SFCT, subfoveal choroidal thickness; SRF, subretinal fluid.

2.3.7.1. Eplerenone

The MR antagonist eplerenone was initially developed for the treatment of heart failure (Pitt et al., 2003). However, as discussed above, both the GR and MR have been hypothesized to play a role in the pathogenesis of CSC, since corticosteroids bind to both receptors (Daruich et al., 2015; Han et al., 2014; van Dijk et al., 2016b; van Dijk et al., 2017b; Zhao et al., 2012). Due to the presence of a 9,11-epoxide group, eplerenone is a more selective MR antagonist than spironolactone and therefore has fewer hormone-associated side effects (Cook et al., 2003; Delyani, 2000; McMahon, 2001). Moreover, eplerenone is far less likely to induce side effects such as gynecomastia and mastalgia compared to spironolactone, particularly in male patients. Other potential side effects of eplerenone include dizziness, nausea, diarrhea, and/or headache, and these treatment-related side effects can occur in up to 22% of patients (van Rijssen et al., 2022). Contraindications for eplerenone include concurrent treatment with potassium-sparing diuretics, potassium supplements, potent CYP3A4 inhibitors, and concurrent use of an angiotensin receptor blocker or angiotensin-converting enzyme inhibitor (Hughes and Cassagnol, 2022).

To date, two relatively large RCTs investigated the efficacy of eplerenone in the treatment of CSC. First, in the VICI trial Lotery and colleagues conducted an investigator-initiated randomized double-blind placebo-controlled trial involving 114 patients with cCSC who received either eplerenone (25 mg/day for 1 week, then increasing to 50 mg/day for up to 12 months) or placebo (Lotery et al., 2020). The primary outcome of this trial was BCVA 12 months after their baseline visit; although BCVA improved from 77 ETDRS letters at baseline to 80 ETDRS letters in the eplerenone group, this was not significantly different from the placebo group, which improved from 78 ETDRS letters at baseline to 80 ETDRS letters. Secondary outcomes of this trial included: low luminance visual acuity; central subfield retinal thickness; change in SRF thickness relative to baseline; systemic and/or ocular adverse events; macular atrophy of the RPE; SFCT; choroidal permeability; time to reach SRF resolution; complete SRF resolution; classification of SRF; resolution as early, late, or none; time to recurrence of SRF; fundus FA phenotype; incidence of CSC in the fellow eye; and patient-reported visual function. None of these secondary outcomes differed significantly between the two groups, with exception of SRF thickness, which was lower in the placebo group at 12 months compared to the eplerenone group. Moreover, 12 months after baseline, 16 out of 54 patients (30%) who received placebo and 8 out of 51 of patients (16%) who received eplerenone had complete SRF resolution on OCT.

Second, Van Rijssen and colleagues performed the SPECTRA trial, a RCT comparing eplerenone to half-dose PDT in 104 patients with cCSC (van Rijssen et al., 2022). Similar to the VICI trial, the eplerenone group received 25 mg/day for one week, during which the serum potassium level was assessed, and this was increased to 50 mg/day depending on the serum potassium level. Three months after baseline, 78% of the PDT-treated patients had complete SRF resolution, compared to only 17%

of patients in the eplerenone group (p<0.001). In contrast, the authors found no significant difference in either mean BCVA between the eplerenone and half-dose PDT groups (83 and 84 ETDRS letters, respectively) or in mean vision-related quality of life scores. Retinal sensitivity on microperimetry, however, increased from 23 to 25 dB in the half-dose PDT group which was a significantly larger increase compared to the eplerenone group, in which retinal sensitivity increased from 23 to 24 dB (p=0.041). Moreover, no treatment-related adverse events were reported in the half-dose PDT group, whereas 22% of patients in the eplerenone group reported adverse events that were potentially treatment-related, including headache, dizziness, rash, paresthesia in the hand or leg, nausea, skin rash, diarrhea, stomach complaints, heart palpitations, general malaise, and fatigue; 15% of patients in this group opted to stop treatment prematurely due to the development of headache, nausea, and/or fatigue.

In addition to the two aforementioned RCTs, several retrospective studies and several smaller prospective studies regarding eplerenone treatment have been performed (see Table 6). For example, Bousquet and colleagues performed a prospective pilot study involving 13 patients with cCSC and found that eplerenone treatment led to a reduction in SRF, as well as improved BCVA and reduced central macular thickness (Bousquet et al., 2013). In a retrospective study of 110 eyes in 83 patients with cCSC, Petkovsek and colleagues found that one year after treatment with eplerenone, 33% of eyes had complete SRF resolution, but they found no significant change in BCVA (Petkovsek et al., 2020). In a prospective case-control study, Venkatesh and colleagues found that patients with aCSC who took oral eplerenone achieved SRF resolution and improved vision more quickly than untreated patients who were simply observed (Venkatesh et al., 2020). However, it is important to keep in mind that some reportedly beneficial results may have occurred due in part to the natural course of CSC, which tends to spontaneously resolve in many aCSC cases, and even in up to 30% of untreated cCSC cases (Lotery et al., 2020). Moreover, assessing the treatment effects and outcome is complicated by the relatively coarse clinical distinction between aCSC and cCSC, which can have overlapping features, as well as marked variability in the classification of these CSC subtypes and CSC in general (Chhablani et al., 2020). Performing studies with a randomized placebo-controlled design such as the VICI trial is therefore essential in order to distinguish the difference between treatment effect vs. placebo and the natural disease course, particularly in the case of CSC (Lotery et al., 2020). Precisely why eplerenone does not appear to be effective in treating cCSC is unclear, but may be due—at least in part—to the relatively low expression of MRs in human choroidal endothelial cells (Brinks et al., 2022a).

In conclusion, although small, non-randomized retrospective studies have shown potentially favorable outcomes following eplerenone treatment for CSC, the results of two recently published large RCTs—namely, the SPECTRA and VICI trials—do not support these previous results (Lotery et al., 2020; van Rijssen et al., 2022). Thus, to date there is insufficient evidence that patients with CSC can

benefit from eplerenone, although other treatment regimens using eplerenone and/or newly developed MR antagonists may provide better results.

2.3.7.2. Spironolactone

The MR antagonist spironolactone is a potassium-sparing diuretic approved for the treatment of primary hyperaldosteronism and congestive heart failure, binding to the distal tubule in the kidney and serving as a binding competitor of aldosterone. Spironolactone is currently the most potent MR antagonist used in clinical practice (Brinks et al., 2018). Side effects have been reported in more than 10% of patients and can include headache, fatigue, gynecomastia, decreased libido, and menstrual disruption (Delyani, 2000). In addition, patients taking spironolactone are at risk for developing hyperkaliemia, which can cause cardiac arrest; therefore, the patient's potassium levels should be monitored during treatment, particularly in at-risk patients with diabetes mellitus, kidney and/or liver disorders, and elderly patients. Because of the increased risk of hyperkaliemia and subsequent cardiac arrhythmia, contraindications for taking spironolactone include the use of other potassium-sparing diuretics, potassium supplements, CYP3A4 inhibitors, and the combined use of an angiotensin receptor blocker and angiotensin-converting enzyme inhibitor.

Relatively few studies investigated the use of spironolactone in CSC. For example, Sun and colleagues conducted a prospective RCT that included 30 eyes in 30 patients with aCSC who were randomized to receive either treatment with spironolactone (40 mg, twice daily) or no treatment (i.e., observation). At 2 months, the authors found that 56% of patients in the spironolactone group had complete SRF resolution compared to only 8% of patients in the untreated group (p=0.018) (Sun et al., 2018). Bousquet and colleagues performed a randomized controlled crossover study involving 15 patients with non-resolving CSC and found a mean reduction in choroidal thickness at 30 days of 102 µm in the patients treated with spironolactone (50 mg daily for 30 days) compared to only 10 µm in patients after taking placebo; however, the authors did not report the rates of complete SRF resolution (Bousquet et al., 2015). Another prospective clinical trial, but without a control group, was performed in 21 eyes in 21 patients with non-resolving CSC who were treated with spironolactone (25 mg, twice daily) for up to 16 weeks (with treatment duration depending on the response) and found that 71% of patients had either a significant improvement or complete resolution of SRF at 12 months (Herold et al., 2017). Finally, Falavarjani and colleagues performed a prospective case series involving 16 eyes in 14 patients with cCSC who were treated with spironolactone (25 mg twice daily) for at least 6 weeks (Falavarjani et al., 2017). The authors found that 44% of eyes achieved complete SRF resolution after a mean follow-up period of 3 months, and mean LogMAR BCVA significantly improved from 0.54 at baseline to 0.42 at final visit (p=0.04). However, it is important to note that similar to the previous study, this study did not include a control group.

In addition to the above-mentioned prospective studies regarding the use of spironolactone for treating CSC, a few retrospective studies have also been performed and have shown beneficial effects such as an improvement in BCVA, reduced choroidal thickness, and reduced SRF (Chai et al., 2016; Chin et al., 2015; Daruich et al., 2016; Herold et al., 2014; Kapoor and Wagner, 2016; Kim et al., 2019a; Kim et al., 2018a; Pichi et al., 2017; Sinawat et al., 2020). For example, Sinawat and colleagues performed a retrospective study of 21 patients with persistent CSC who received spironolactone (25 mg twice daily) for a mean duration of 4.9 months and compared the outcome with 41 patients who received conservative treatment (including oral vitamin B supplements and/or minor tranquilizer medication) (Sinawat et al., 2020). Six months after baseline, 57% of the spironolactone-treated patients had complete SRF resolution on OCT, compared to only 32% in the conservative treatment group (p=0.032). In addition, BCVA improved significantly in the spironolactone-treated group (p<0.05), but not in the conservative treatment group, although it should be noted that the patients in the conservative treatment group had better—albeit not significant—BCVA at baseline compared to the spironolactone group (0.27 vs. 0.47 LogMAR, respectively, p=0.06). Recurrence of SRF after complete resolution occurred in 33% and 31% of the spironolactone and conservative treatment groups, respectively (Sinawat et al., 2020). Kim and colleagues retrospectively compared 26 eyes in 26 patients with non-resolving CSC who were treated with spironolactone to 24 eyes in 24 patients who received half-dose PDT (Kim et al., 2019a). At 12 months, 69% of the patients in the spironolactone had complete SRF resolution, which was not significantly different than in the half-dose PDT group (88%). Moreover, the authors found no significant difference at 12 months with respect to BCVA or SRF height. In contrast, the recurrence rate was significantly higher in the spironolactone group compared to the half-dose PDT group (p=0.002), presumably because PDT has a more lasting remodeling effect on the dysfunctional choroid in CSC. Finally, a retrospective study involving 17 eyes in 15 patients with steroid-induced CSC found complete SRF resolution in 82% of eyes treated for at least 1 month with spironolactone (50 mg once daily); however, it is important to note that the use of systemic steroids was discontinued in all patients during spironolactone treatment (Kim et al., 2018a).

In summary, there is currently insufficient evidence in the form of large RCTs to optimally evaluate the putative benefits of spironolactone in the treatment of CSC, despite potentially promising results from some studies. In addition, more long-term follow-up data are needed in patients with CSC in order to assess treatment durability and the risk of recurrence risk, for example compared to placebo and PDT.

2.3.7.3. Mifepristone

Mifepristone (commonly known as RU-486) is a high-affinity GR and progesterone receptor antagonist currently approved to pharmaceutically induce abortion in early pregnancy (Cadepond et

al., 1997; Clark, 2008). As noted above, studies have has shown that corticosteroid use is the most significant external risk factor for developing CSC (Haimovici et al., 2004), and stimulation of GR, one of the receptors to which corticosteroids bind, may play a role in the pathogenesis of CSC (Brinks et al., 2022a). Therefore, mifepristone has been suggested as a possible treatment option for CSC based on the rationale that it can inactivate the cytosolic GR complex. However, to date only one study has been performed regarding the use of mifepristone for the treatment of CSC. Specifically, Nielsen and colleagues performed a prospective study involving 16 patients with cCSC who received mifepristone (200 mg daily for up to 12 weeks) (Nielsen and Jampol, 2011). The authors found an improvement in BCVA of ≥5 ETDRS letters in 5 patients (31%), with no severe adverse events reported; however, the authors did not report the percentage of patients who achieved complete SRF resolution.

2.3.8. Other systemic treatments

2.3.8.1. Antioxidants

Treating CSC with high-dose antioxidants was evaluated in a small number of studies. First, a randomized placebo-controlled trial that included 29 patients with aCSC who received high-dose antioxidants tablets containing vitamins A, C and E, riboflavin, zinc, copper, selenium, manganese and lutein/zeaxanthin) found that 22 patients (76%) had complete SRF resolution 3 months after baseline, compared to only 14 out of 29 patients (48%) who received placebo (p=0.027) (Ratanasukon et al., 2012). In contrast, there was no significant difference with respect to the improvement in BCVA. Notably, during this trial patients were able to receive additional treatments as needed, including laser photocoagulation and PDT, which complicated the analysis.

Curcumin (diferuloylmethane), is an herbal compound with antioxidant and anti-inflammatory properties (Reddy et al., 2020). In a pilot study by Mazzolani followed by a larger study by Mazzolani et al., oral curcumin was found to reduce the height of the neuroretinal or neuroretinal detachment in 78% of 12 patients with either aCSC or cCSC 6 months after treatment (Mazzolani, 2012; Mazzolani and Togni, 2013). However, no information regarding complete SRF resolution was provided. In summary, there is currently not enough evidence available to support the use of antioxidants for treating CSC.

2.3.8.2. Aspirin

Patients with cCSC can present with increased plasma concentrations of plasminogen activator inhibitor 1 compared to healthy controls, suggesting a possible role in CSC pathogenesis (Iijima et al., 1999). Aspirin (acetylsalicylic acid) is an anti-aggregant and may therefore help to reduce the levels of plasminogen activator inhibitor 1, benefitting patients with CSC. To test this hypothesis, Caccavale

et al. performed prospective case series that included 109 patients with aCSC or cCSC who were treated with low-dose aspirin and found that treatment appeared to increase the rate of visual improvement, with fewer recurrences, compared to 89 patients in an historical control group; however, the authors' use of an historical group as a control should be considered when interpreting these results (Caccavale et al., 2010). Thus, to date only a limited amount of evidence supports the idea that aspirin may be used as an appropriate treatment for CSC.

2.3.8.3. Beta-blockers

Three decades ago, Browning et al. previously conducted a small RCT in which 8 patients with CSC received the beta-blocker naladol while another 8 patients received placebo (Browning, 1993). After 4 months, the amount of serous SRF accumulation decreased to a lesser extent in the nadolol-treated patients compared to the patients who received placebo (with an average decrease of 4.3 mm^2 vs. 16.0 mm^2, respectively), although this difference was not significant. In a subsequent case report, Tatham and Macfarlane described two patients with CSC who had complete SRF resolution after treatment with the beta-blocker metoprolol (Tatham and Macfarlane, 2006).

In 2015, a prospective double-masked study was carried out involving 23 patients with aCSC who were treated with metipranolol (10 mg twice daily) and 25 patients who received placebo (Chrapek et al., 2015). The authors found no statistically significant difference between the two groups with respect to the time to reach complete SRF resolution. Finally, in a recent RCT Chen et al. compared treatment with propranolol against placebo in 120 patients with unspecified CSC (with 60 patients in each group) (Chen et al., 2020). The authors found that mean time to reach complete SRF resolution was significantly shorter in the propranolol group compared to the placebo group (1.9 months vs. 3.5 months, respectively, p=0.008). In addition, at 4 months complete SRF resolution was achieved in 57 out of 60 patients (95%) in the propranolol group compared to 47 out of 60 patients (78%) in the placebo group (p=0.001). However, it is important to given the high percentage of patients in the placebo group who achieved complete SRF resolution, this study may have included primarily patients with more a focal, aCSC-like phenotype.

Based on the inconclusive and contrasting results in these studies and reports, additional studies are needed before beta-blockers can be considered a viable treatment option for CSC.

2.3.8.4. Carbonic anhydrase inhibitors

Wolfensberger et al. first proposed that the absorption of SRF through the RPE may be improved by acidifying the subretinal space using carbonic anhydrase inhibitors (Wolfensberger et al., 1999). A subsequent prospective non-randomized comparative trial by Pikkel et al. involving 15 patients with CSC who were treated with acetazolamide and 7 untreated control patients found that acetazolamide

accelerated both the improvement of subjective complaints and SRF resolution, but had no effect on either final visual acuity (VA) or the rate of recurrence (Pikkel et al., 2002). In a recent prospective non-randomized controlled intervention study, Liew et al. treated 18 patients with cCSC with topical dorzolamide for 3 months and compared the results to 15 untreated patients (Liew et al., 2020). At 3 months, a significantly higher percentage of dorzolamide-treated patients achieved complete SRF resolution compared to the untreated patients (78% vs. 40%, respectively); however, the authors found no significantly difference between groups with respect to the change in BCVA.

To date, no large RCTs have been performed to investigate whether patients with CSC can benefit from treatment with carbonic anhydrase inhibitors. Therefore, additional evidence is needed before carbonic anhydrase inhibitors can be considered a viable treatment for CSC.

2.3.8.5. Finasteride

Finasteride inhibits the enzyme 5-alpha-reductase, which converts testosterone to dihydrotestosterone, and is currently used for the treatment of benign prostatic hyperplasia, prostate cancer, and hair loss. Because androgens such as testosterone have been suggested to play a role in CSC (Brinks et al., 2022d), finasteride tested as a possible treatment for CSC in two studies. First, Forooghian et al. performed a prospective pilot study in which 5 patients with cCSC took finasteride (5 mg daily) for 3 months (Forooghian et al., 2011). However, the authors reported no change in mean BCVA, and SRF resolution was not reported. Subsequently, Moisseiev et al. performed a retrospective review of 29 eyes in 23 patients with cCSC who were treated with finasteride (Moisseiev et al., 2016). The authors found a significant decrease in the presence of SRF at both 1 month and 3 months, with 75.9% of patients achieving complete SRF resolution at their final visit, with a mean follow-up period of 14.7 months. In addition, VA was improved significantly at the final follow-up visit. Despite these potentially encouraging results, well-designed RCTs are needed in order to determine whether or not finasteride can serve as a potential treatment for CSC.

2.3.8.6 Sildenafil

Recently, a handful of studies investigated whether sildenafil citrate (Viagra), which is primarily prescribed for erectile dysfunction and pulmonary hypertension, can be used for the treatment of CSC. Sildenafil is believed to increase blood flow to the choroid by inhibiting the enzymes phosphodiesterase 5 (PDE5) and phosphodiesterase 6 (PDE6), as shown by measuring choroidal thickness in healthy volunteers using both ultrasound and OCT (Kim et al., 2013a). Concerns that sildenafil can cause ocular adverse events, including CSC, have been countered by post-marketing surveillance data (French and Margo, 2010). Recently, Breazzano et al. performed a small prospective study involving 4 patients with cCSC (Breazzano et al., 2020). Following treatment with sildenafil,

SRF resolved in 2 patients together with improvement in choroidal thickness, but not in the other 2 patients. The authors noted, however, that the two non-responding patients had a longer history of CSC at enrollment; moreover, one of these patients received prior PDT treatment, while the other previously responded intravitreal anti-VEGF therapy (Breazzano et al., 2020). In addition, Coleman et al. presented a case report in which a patient with long-standing CSC was treated with sildenafil, after which the SRF disappeared. After treatment was stopped, SRF recurred; SRF again resolved rapidly after resuming treatment, corresponding to the so-called "challenge-dechallenge-rechallenge" paradigm and supporting the hypothesis of a temporal cause-and-effect relationship (Coleman et al., 2021).

Interestingly, sildenafil has also been reported as a possible risk factor for CSC in some studies, although the evidence is relatively limited (Aliferis et al., 2012; Etminan et al., 2022; Quiram et al., 2005). Based on the limited amount of data available regarding the use of sildenafil for the treatment of CSC, larger studies may be needed in order to establish whether sildenafil can be beneficial in select patients with CSC.

2.3.8.7. Eradication of *Helicobacter pylori* infection

Helicobacter pylori infection has also been suggested as a risk factor for CSC (Chatziralli et al., 2017). This bacterial infection is typically treated using a proton pump inhibitor in combination with antibiotics such as clarithromycin, amoxicillin, and/or metronidazole (FitzGerald and Smith, 2021; Zavoloka et al., 2016). To date, only a handful of small retrospective studies examined the effects of eradicating *H. pylori* in order to treat CSC, yielding inconsistent results (Dang et al., 2013; Rahbani-Nobar et al., 2011; Zavoloka et al., 2016). Thus, the currently available evidence does not support the idea that eradicating *H. pylori* can serve as a viable treatment strategy in CSC.

2.3.8.8. Ketoconazole

The antifungal compound ketoconazole also inhibits the enzymes that produce androgens and glucocorticoids. Ketoconazole may also reduce endogenous cortisol levels due by inhibiting GRs antagonism and adrenal biosynthesis and may therefore have clinical value in the treatment of CSC. To date, however, only two studies have evaluated the effect of ketoconazole in CSC. In a pilot case-controlled study by Golshahi et al., 15 patients with aCSC received ketoconazole (200 mg/day) for 4 weeks, and the results were compared with 15 untreated patients with aCSC (Golshahi et al., 2010). The authors found no significant differences between the two groups with respect to the improvement in VA or the decrease in either SRF or PED. Two patients in the ketoconazole group discontinued treatment, one due to erectile dysfunction and another due to nausea (Golshahi et al., 2010). In addition, Meyerle and colleagues studied the effect of ketoconazole (600 mg daily) for 4 weeks in 5

patients with cCSC and found no change in median VA at 8 weeks (Meyerle et al., 2007). Given the sparsity of data, there is insufficient evidence to support the use of ketoconazole in CSC.

2.3.8.9. Melatonin

The hormone melatonin regulates the circadian rhythm and has been proposed to improve outcome in CSC (Pandi-Perumal et al., 2008). To test this hypothesis, Gramajo and colleagues performed a prospective comparative case series in which 8 patients with cCSC received melatonin (3 mg, 3 times a day), and another 5 received placebo (Gramajo et al., 2015). Interestingly, the patients who received melatonin showed an improvement in BCVA, in contrast to the patients who received placebo. In addition, 3 of the 8 patients (37.5%) of the melatonin-treated patients had complete SRF resolution at 1 month. However, this study was limited by its small sample size, and the percentage of patients who experienced complete SRF resolution was relatively low; therefore, additional evidence in the form of a large RCT is needed.

2.3.8.10. Methotrexate

Methotrexate (MTX) is an antimetabolite and immunosuppressant commonly used to treat both systemic and ophthalmic inflammatory conditions. Due to its ability to interact with steroid receptors, MTX has been suggested as a possible treatment for CSC (Kurup et al., 2012). To date, two studies test this hypothesis in patients with cCSC, and both studies found that BCVA improved significantly after treatment with oral low-dose MTX for 12 weeks (Abrishami et al., 2015; Kurup et al., 2012). In the first study, Abrishami and colleagues performed a prospective, non-controlled clinical trial involving 23 patients and found that 13 patients (62%) achieved complete SRF resolution after 6 months on MTX (Abrishami et al., 2015). In the second study, Kurup and colleagues retrospectively analyzed 9 patients with cCSC treated with low-dose MTX and found complete SRF resolution in 83% of patients after an average treatment duration of 12 weeks (Kurup et al., 2012). Despite these encouraging results, no large RCTs have been conducted to support the use of MTX as a treatment for CSC. In addition, MTX can cause severe side effects, including bone marrow suppression (myelosuppression) and pulmonary, hepatic, and renal toxicity.

2.3.8.11. Nonsteroidal anti-inflammatory drugs

The non-steroidal anti-inflammatory drug (NSAID) nepafenac (0.1%) has also been proposed for treating aCSC. In a retrospective study by Alkin et al., 17 eyes in 16 patients with aCSC were treated with topical nepafenac (3 times daily for 4 weeks), while 14 eyes in 14 patients did not receive any treatment (Alkin et al., 2013). At 6 months, 82.3% of nepafenac-treated patients had complete SRF resolution, compared to 42.8% of patients in the untreated group (p=0.02). In addition, mean BCVA

significantly improved in the nepafenac-treated group (from 0.19 LogMAR at baseline to 0.09 LogMAR at 6 months; p=0.01); in contrast, mean BCVA was unchanged between baseline and 6 months in the untreated group (0.13 vs. 0.1, respectively, p=0.28). In addition, Wuarin et al. performed a pilot study to compare the effect of oral acetazolamide combined with topical nepafenac with untreated patients (Wuarin et al., 2019). The authors found that the treated group achieved SRF resolution more quickly than the untreated group (p<0.05), but found no functional benefit with respect to BCVA at 4 months, with 0.8 Snellen in the treated group compared to 0.9 for the control group. Finally, Bahadorani and colleagues performed a retrospective review of 27 patients with CSC, in which 14 patients were treated with topical NSAIDs and 13 patients were untreated (Bahadorani et al., 2019). The authors found that 64.3% percentage of treated patients experienced a reduction of SRF volume, compared to only 11.1% of untreated patients (p<0.02). Moreover, 50% of the treated patients achieved complete SRF resolution compared to only 15% of untreated patients. However, they found no significant difference between the two groups with respect to the increase in VA (p=0.067)

The aforementioned studies were relatively small and should therefore be followed up by large RCTs in order to determine whether NSAIDs should be pursued as a potential treatment for CSC.

2.3.8.12. Rifampicin

Rifampicin (also known as rifampin) is an antibiotic with anti-oxidative and anti-apoptotic properties. When taken orally, it can affect endogenous steroid metabolism by upregulating the cytochrome P450 enzyme 3A4 in the liver (Guengerich, 1999). Several studies investigated rifampicin for use in CSC, although none of these were randomized placebo-controlled clinical trials. First, a prospective single-arm study found that rifampicin (300 mg twice daily for 3 months) caused SRF resolution in 4 out of 14 eyes (29%) in patients with cCSC after 6 months; treatment was discontinued in two patients due to adverse events (Shulman et al., 2016). A subsequent retrospective study of patients with cCSC who were treated with rifampicin found that all 4 out of 9 eyes with focal leakage on FA (44%) had complete SRF resolution after a follow-up of 3 months; in contrast, 4 out of 5 eyes with diffuse leakage on FA (80%) had persistent SRF (Venkatesh et al., 2018b). In addition, Khan et al. performed an observational clinical study that included 38 eyes in 31 patients with unspecified CSC and found that patients taking rifampin (300 mg once daily for 3 months) had an improvement in mean BCVA from 0.56 at baseline to 0.47 LogMAR measured 4 weeks after treatment (i.e., 4 months after baseline) (Khan et al., 2016). Lastly, a RCT performed by Loya et al. compared two dosing regimens of rifampicin (600 mg once daily for 1 month vs. 300 mg once daily for 3 months) in a total of 91 eyes in 80 patients (Loya et al., 2019). One month after the start of treatment, the patients who received 300 mg rifampicin had a larger improvement in VA compared to the patients who received 600 mg, although this difference was no longer present after 3 months. Further research regarding the

feasibility of using rifampicin to treat CSC has low priority, given the side effects and modest putative response in these patients.

2.3.9. Other treatment modalities

In addition to the extensive list of treatment modalities tested for CSC, several relatively small studies have investigated other, non-conventional treatments such as wearing an eye patch (Earl et al., 2014; Zhao et al., 2021), sub-tenon injection of platelet-rich plasma with retinal electromagnetic stimulation (Arslan and Özmert, 2020), the anti-lipemic drug fenofibrate (Chai et al., 2016), intravitreal injections of the antioxidant dobesilate (Cuevas et al., 2012), brachytherapy (Arora et al., 2022), and acupuncture (Lu and Friberg, 1987). Meditation has also been proposed as a therapy for CSC, as stress has been reported as a risk factor for CSC in several studies (Gelber and Schatz, 1987; Lahousen et al., 2016). Recently, Nongrem et al. conducted a small pilot study in which 40 patients diagnosed with acute or non-resolving CSC were randomly assigned to either practice meditation or receive routine care (Nongrem et al., 2021). Interestingly, the mean time to achieve complete SRF resolution was 9.4 ± 4.2 weeks in the meditation group, significantly shorter than in the non-routine care group (19.5 ± 2.8 weeks, $p<0.001$). At 4 months, CSC remained in 60% of patients in the routine care group, compared to only 8% of patients in the meditation group. In addition, that patients in the medication group had significant improvements in both systolic and diastolic blood pressures (Nongrem et al., 2021). Despite these promising preliminary results, a caveat of this study was that a relatively large number of patients (8 out of 20) in the meditation group failed to complete the required training and were therefore excluded from the analysis. Nevertheless, a large prospective RCT involving participants who are motivated to complete the meditation training should be conducted in order to test whether or not meditation can benefit patients with CSC.

3. Evidence-based treatment strategies for CSC

Here, we summarize the treatment strategies for CSC subtypes based on the currently available evidence. The treatment of CSC should be based primarily on conclusive evidence obtained from large RCTs with long-term follow-up. The variable clinical presentation and natural course of CSC, waxing and waning SRF, and the spontaneous resolution of SRF (which is common in aCSC and can also occur in up to 30% of cCSC cases) underscore the importance of high-level evidence-based treatment (Lotery et al., 2020; van Rijssen et al., 2020a; van Rijssen et al., 2019b). These clinical features also make the interpretation of evidence obtained from retrospective and/or small studies regarding CSC treatment challenging and often unreliable. The ability to accurately interpret evidence regarding treatment efficacy in CSC is further complicated because CSC has been traditionally classified as either aCSC or cCSC, with the distinction based largely on the duration of symptoms, as well as the presence or absence of more extensive atrophic RPE changes. To date, the lack of a validated classification system has complicated studies regarding the natural disease progression, the preferred treatment, the spontaneous resolution of SRF, and the clinical course of CSC among disease subtypes, all of which be important for determining a prognosis and in the design of and outcomes in interventional trials (Daruich et al., 2015; Feenstra et al., 2022a; Mohabati et al., 2018c; Otsuka et al., 2002). Recently, a novel classification system was proposed in which CSC can be divided into more extensive subgroups such as simple CSC, complex CSC, and atypical CSC (Chhablani et al., 2020). This recent classification system also accounts for complications such as persistent SRF, outer retinal atrophy, intraretinal fluid, and the presence or absence of MNV. If validated, future RCTs should consider using this classification, and it should be uses in clinical practice, providing detailed insights into the treatment outcomes achieved for specific clinical subtypes. This may be challenging to realize, however, as CSC is relatively rare and studies to date regarding the treatment of CSC have all been investigator-initiated, with the inherent challenges associated with such studies. It has also been suggested that each CSC subgroup may require a specific treatment strategy (Daruich et al., 2015), although the superiority of one treatment over another (for example, half-dose PDT over HSML) has been shown in both the focal and diffuse phenotypes of cCSC (van Rijssen et al., 2019a). Given that CSC typically presents at a relatively young age and has a relatively benign course, safety remains the top priority when developing new treatment strategies for this chorioretinal disease (Daruich et al., 2015; Mohabati et al., 2020b; Otsuka et al., 2002).

3.1 Acute CSC

A flowchart summarizing the decision-making process in the treatment of aCSC is shown in Fig. 7. With aCSC—particularly in patients with a single focal leak and minimal (i.e., smaller than 1-disc diameter) atrophic RPE changes—observation is the most commonly used and recommended strategy during the first 4 months, given the high rate of spontaneous SRF resolution during this time frame

(Klein et al., 1974; Yannuzzi, 2010). However, for patients who require rapid SRF resolution and restoring of visual function—for example, for professional reasons— treatment can be performed soon after presentation. Despite the high likelihood of spontaneous SRF resolution in aCSC, retinal damage may still occur in the early stages and can progress if the SRF does not resolve (Hata et al., 2013). Moreover, SRF can be so shallow that it cannot be detected on slit-lamp biomicropscopy (Wang et al., 1999), and OCT imaging is therefore critical for diagnosing and monitoring CSC. Importantly, residual SRF can still cause photoreceptor and/or RPE atrophy, as well as subsequent vision loss over a period of years (Wang et al., 2002).

The treatment for aCSC should focus on restoring visual function and improving the visual prognosis by achieving complete SRF resolution, as well as preventing SRF recurrence and progression to cCSC (Mohabati et al., 2020a).

In specific cases in which a focal leak on FA is located at a relatively safe distance from the fovea, argon laser photocoagulation can be used to achieve complete SRF resolution (Chhablani et al., 2014; Leaver and Williams, 1979; Sun et al., 2020; van Dijk et al., 2022b; Zhou et al., 2021). However, underlying choroidal abnormalities in aCSC should not be treated using thermal laser photocoagulation. Furthermore, this treatment modality can have risks such as development of a symptomatic paracentral scotoma, MNV, and/or formation of a chorioretinal adhesion with secondary intraretinal cystoid fluid.

Several studies have shown that half-dose PDT is a good treatment option for aCSC, with a shorter time to achieve SRF resolution and a more rapid recovery of retinal sensitivity compared to placebo (Chan et al., 2008; Lu et al., 2016; Ober et al., 2005; Tsai and Hsieh, 2014). In addition, retrospective studies have shown that the risk of recurrence of SRF leakage in aCSC is lower following PDT (Lu et al., 2016; Mohabati et al., 2020a; Nicholson et al., 2013; Ober et al., 2005). On the other hand, opting for a short observation period of a few months does not appear to affect longer-term outcome in aCSC (Kim et al., 2014; Missotten et al., 2021). Based on the available evidence, performing half-dose PDT within 4 months of presentation may be the treatment of choice in patients with recurrent active aCSC, patients with bilateral aCSC, and patients with aCSC who rely on their vision for professional reasons. In addition, ICGA-guided half-dose PDT may be the method of choice in aCSC, as this method can optimally treat the underlying choroidal abnormalities. With respect to the PDT settings, half-dose PDT may be preferred over half-fluence PDT and half-time PDT, as large RCTs have shown that half-dose is highly efficacious in cCSC, and using half the standard dose can minimize both local and systemic side effects (even though these side effects are relatively rare with all PDT protocols) (Feenstra et al., 2023; van Dijk et al., 2018b; van Rijssen et al., 2022). In addition, because each treatment uses half the standard dose of verteporfin, a single vial of verteporfin can be used to treat two patients, reducing costs and increasing the availability of verteporfin in times of scarcity (Sirks et al., 2022).

3.2 Chronic CSC

The goal when treating cCSC is to reverse the photoreceptor and RPE dysfunction, and to stop or even prevent irreversible progressive photoreceptor damage caused by persistent SRF, as this can lead to irreversible vision loss and reduced vision-related quality of life (Breukink et al., 2017a; Deng et al., 2021; Mohabati et al., 2020a; Mrejen et al., 2019; Nicholson et al., 2013). Currently, PDT, argon laser photocoagulation, eplerenone, and HSML are the most commonly used treatments for cCSC. A flowchart depicting the decision-making process for treating cCSC is shown in Fig. 8.

Two large RCTs and numerous large retrospective studies investigated the use of half-dose PDT in cCSC, showing that 21-100% of patients with cCSC achieve complete SRF resolution following PDT (Lai et al., 2016; Nicolo et al., 2012; Scholz et al., 2016; Stewart, 2006; Tseng and Chen, 2015). In addition, the PLACE trial found that half-dose PDT led to complete SRF resolution and functional improvement in significantly more patients compared to HSML (van Dijk et al., 2018b), while the SPECTRA trial found that half-dose PDT led to complete SRF resolution and functional improvement in significantly more patients compared to treatment with the MR antagonist eplerenone (van Rijssen et al., 2022). Importantly, PDT does not cause permanent damage to the choriocapillaris (Rabiolo et al., 2018) and has an excellent short-term and long-term safety profile, even when including the fovea in the treatment spot (Feenstra et al., 2023; Silva et al., 2013; van Rijssen et al., 2021b).

In some cases, or if PDT is not available, laser photocoagulation can be considered—particularly if the focal leak on FA is located at a relatively safe distance from the central macula—and may lead to rapid, complete SRF resolution, at least over the short term (Leaver and Williams, 1979). A recent meta-analysis by Van Dijk and colleagues found a significant, high odds ratio for short-term complete SRF resolution when using conventional laser (van Dijk et al., 2022b), which is consistent with retrospective cohort studies (Chhablani et al., 2014; Zhou et al., 2022a). However, unlike PDT, argon laser photocoagulation does not target the underlying choroidal leakage and dysfunction, and it carries risks such as causing a symptomatic paracentral scotoma, MNV, and/or chorioretinal adhesions with secondary intraretinal cystoid fluid. In addition, although only a minority of cCSC cases have leakage points that are exclusively extrafoveal, argon laser photocoagulation may be a viable option in these cases, when access to PDT may be limited, and when costs related to treatment may be a factor in guiding the treatment decision (van Dijk et al., 2022b). However, and again unlike PDT, the long-term outcome following argon laser photocoagulation is not superior to untreated controls, and only a limited number of studies have been conducted to investigate this issue (Gilbert et al., 1984).

The PLACE trial found that ICGA-guided half-dose PDT was superior to ICGA-guided 810-nm HSML in cCSC in terms of complete SRF resolution both short-term (i.e., 6-8 weeks post-treatment), with 51% versus 14% of patients, respectively, and long-term (i.e., 7-8 months post-treatment), with

67% versus 29% of patients, respectively (van Dijk et al., 2018b). In addition, the increase in both BCVA and retinal sensitivity on microperimetry was significantly larger in the half-dose PDT group compared to the HSML group (van Dijk et al., 2018b). A long-term follow up study found that 20 months after treatment, patients with cCSC who were successfully treated with half-dose PDT were less likely to have a recurrence of SRF compared to patients who were successfully treated with HSML (van Rijssen et al., 2021b). Moreover, patients with cCSC with a focal leakage spot on FA appear to have a more favorable outcome than patients with diffuse leakage after HSML treatment (Chen et al., 2008). Analyzing the effects of treating cCSC with HSML is also complicated by the wide range of treatment regimens, laser settings, and wavelengths used in various studies (Wood et al., 2017).

Treating cCSC with MR antagonists has been shown to induce complete SRF resolution in 31-67% of patients based on a few large (i.e., >50 patients), non-randomized retrospective studies, with eplerenone having similar efficacy as spironolactone but a better safety profile (Chai et al., 2016; Daruich et al., 2016; Petkovsek et al., 2019). On the other hand, two large RCTs (namely, the SPECTRA and VICI trials) found relatively low efficacy of eplerenone compared to placebo (Lotery et al., 2020); moreover eplerenone was similar to half-dose PDT, with only 16% and 17% eplerenone-treated patients achieving complete SRF resolution on OCT after 15 months (Lotery et al., 2020; van Rijssen et al., 2022). Thus, the evidence currently available from large RCTs do not support the notion that patients with cCSC can benefit from treatment with MR antagonists.

In summary, based on the currently available data, half-dose (or half-fluence) PDT appears to be the safest and most effective treatment for cCSC; however, PDT is not available in all countries. It should be noted, that while half-dose PDT with verteporfin is the most effective treatment option available, it is more expensive than other treatments and requires a specific laser device. Moreover, the results obtained from large RCTs indicate that half-dose PDT may be the preferred PDT treatment strategy in cCSC, as delivering half of the dose can minimize the risk of local and systemic side effects, although this risk is admittedly small regardless of the PDT protocols (Chan et al., 2008; Feenstra et al., 2023; Park et al., 2021; van Dijk et al., 2018b; van Rijssen et al., 2022; Vasconcelos et al., 2013). In addition, as mentioned above using half the dose of verteporfin can allow the practitioner to treat two patients using one vial, reducing cost and increasing the availability of verteporfin (Sirks et al., 2022). Both recurrent SRF and persistent SRF following PDT have been associated with male gender, diffuse leakage on FA, absence of an intense hyperfluorescent area on ICGA, higher age, and lower baseline BCVA (van Dijk and Boon, 2021; van Rijssen et al., 2018b). In addition, although patients with pre-existing fovea-involving atrophy can achieve SRF resolution following PDT, they are not likely to benefit in terms of improved visual function; however, achieving complete SRF resolution can still prevent these patients from experiencing a further decline in BCVA (van Rijssen et al., 2021c).

Notably, PDT may also be considered in patients with symptomatic cCSC who present with extrafoveal SRF (van Dijk et al., 2017a).

In situations in which half-dose PDT is too costly or is unavailable—for example, during the recent period in which verteporfin was in short supply—other treatment options can be considered (Sirks et al., 2022). The choice of treatment should be evaluated on a case-by-case basis, as compelling evidence supporting the efficacy of treatments other than PDT is currently lacking; however, these treatment options may include argon laser photocoagulation in cases with an extramacular focal leakage point on FA. In some cCSC cases, no treatment might be the best option, as one recent study suggested that a specific shape of the SRF in the foveal scan on OCT—the so-called "Fuji sign"—and fewer leakage points on FA are associated with a higher likelihood of achieving spontaneous SRF resolution in these patients (Feenstra et al., 2022a).

3.2.1 Chronic CSC complicated by macular neovascularization

Macular MNV is a relatively common complication in prolonged cases of CSC, and is more prevalent in patients with severe cCSC (Peiretti et al., 2015). Indeed, the presence of MNV has been described in up to 39% of patients with cCSC (Fung et al., 2012; Guo et al., 2021a; Liu et al., 2021; Loo et al., 2002; Nicholson et al., 2018; Peiretti et al., 2018; Peiretti et al., 2015; Savastano et al., 2021; Shiragami et al., 2018; Spaide et al., 1996a). In CSC cases, higher age, female gender, poor baseline vision, prolonged disease, a wider PED at diagnosis, leakage sites within the fovea on FA, and recurrent disease episodes are risk factors for developing secondary MNV (Chhablani et al., 2015; Guo et al., 2021b; Liu et al., 2021; Yeo et al., 2020; Zhou et al., 2022b). MNV secondary to cCSC can be identified using various conventional multimodal imaging techniques such as OCT, FA, and ICGA. However, even with these techniques MNV can be challenging to diagnose, particularly in the early stages; thus, OCT-A can have added value when diagnosing MNV in CSC (Bonini Filho et al., 2015; Hagag et al., 2021; Romdhane and Mantel, 2019).

Several findings on multimodal imaging can suggest MNV in CSC (see Fig. 6), including: *i*) a flat, irregular PED (FIPED) on OCT, which can be recognized as a "double layer sign" (a recognizable and separated line between the RPE and Bruch's membrane line) in combination with mid-reflective to hyperreflective material between RPE and Bruch's membrane; *ii*) a well-demarcated hyperfluorescent lesion on ICGA; and *iii*) diffuse, indistinct leakage of fluorescein and diffuse RPE alterations on FA (Guo et al., 2021a). Although the presence of a FIPED may indicate the presence of MNV, the FIPED can also be avascular, and OCT-A can be helpful for differentiating between a vascularized FIPED (corresponding to type 1 MNV) and avascular variants (Faghihi et al., 2021). Compared to an avascular FIPED, a vascular FIPED typically has a higher SFCT and a lower choroidal vascularity index (defined as the percentage of the luminal area relative to the total

choroidal area), which may help differentiate between these two variants (Faghihi et al., 2021). OCT-A can also be used to measure the quality and quantity of MNVs in CSC (Guo et al., 2021b). Because up to two-thirds of patients with CSC who develop MNV also have a component of polypoidal choroidal vasculopathy (i.e., aneurysmal type 1 neovascularization, which is often seen at the edge of the choroidal vascular network), ICGA is a particularly valuable tool for identifying and localizing these lesions (Peiretti et al., 2015; Peiretti et al., 2019). Adequate diagnosis and treatment of MNVs in CSC is important given that it changes management and is associated with a worse visual outcome (Loo et al., 2002; Sulzbacher et al., 2019).

CSC complicated by an active subretinal MNV is usually treated with intravitreal anti-VEGF injections, which may be combined with half-dose PDT to treat the associated CSC component.

Previous studies have shown variable degrees and incomplete efficacy when treating CSC complicated by MNV with anti-VEGF compounds, with complete SRF resolution achieved in 43-83% of patients (Chhablani et al., 2015; Jung et al., 2019a; Lai et al., 2018; Lejoyeux et al., 2021; Peiretti et al., 2018; Romdhane et al., 2020; Schworm et al., 2020; Song et al., 2021) (Table 7). This finding may be due to the relatively low disease activity of MNV, with the CSC background serving as the primary cause of the SRF. The MINERVA study, a RCT in which patients with MNV secondary to various causes (angioid streak, post-inflammation, CSC, idiopathic, or other) received either intravitreal injections of ranibizumab (119 patients) or sham injections (59 patients), found that ranibizumab was less effective at improving BCVA at 12 months in patients with CSC-associated MNV compared to other causes (Lai et al., 2018). In addition, a retrospective study of 21 eyes in 21 patients with cCSC and MNV found that an extended upload phase of 6 consecutive anti-VEGF injections significantly decreased PED dimensions and increased the resorption of SRF (Schworm et al., 2020). Putative predictors of good treatment response to anti-VEGF therapy have also been identified and include female gender, higher CRT at baseline, a larger amount of SRF, recent appearance of SRF, and a large pretreatment size and flow area of MNV on OCT-A (Romdhane et al., 2020).

Guo et al. recently performed a retrospective case series of 21 eyes with cCSC complicated with type 1 MNV and FIPED on OCT, and found that mean LogMAR BCVA improved from 0.49 at baseline to 0.25 6 months after treatment with half-dose PDT monotherapy; in addition, SRF was resolved in all 21 eyes at 6 months (Guo et al., 2021b). In another retrospective study, Kamimura and colleagues analyzed of 21 eyes in 21 patients with cCSC complicated by MNV and 67 eyes in 67 patients with cCSC without MNV, all of whom were treated with half-time PDT (Kamimura et al., 2023). The authors found that 24 months after treatment, complete SRF resolution was achieved in 76% of patients with MNV at baseline, compared to 91% of patients without MNV; moreover, recurrent and persistent SRF were significantly more prevalent among the patients with MNV compared to patients without MNV (54% vs, 22%, respectively, p=0.013). A previous study by Peiretti et al. found that

combination therapy using both PDT and intravitreal anti-VEGF injections may be a viable treatment option for CSC complicated by type 1 MNV, particularly in cases that present with an associated PCV component (Peiretti et al., 2018). However, additional treatment during follow-up may be required in eyes with MNV (Kamimura et al., 2023). Interestingly, Mandadi and colleagues found that in up to 23% patients with cCSC with evidence of MNV in the affected eye, the fellow eye had a vascular network visible on OCT-A that could not be detected using conventional imaging modalities, including OCT, FA and/or ICGA (Mandadi et al., 2021); moreover, SRF was present in only one-third of these fellow eyes with a vascular network on OCT-A. The precise relevance of this finding is currently unknown, and more research is needed in order to determine the contribution of this so-called “silent type 1 MNV” to the development of subretinal leakage and the occurrence of vision loss at follow-up.

2214 **Table 7.**

2215 Overview of studies that assessed intravitreal injections of anti-VEGF for the treatment of CSC complicated by MNV

Study	CSC subtype	Study design	Mean age (years)	Drug and treatment strategy	Number of eyes	Follow-up (months)	Complete resolution of subretinal fluid (%) at final follow-up	Reported parameters and outcomes
(Chhablani et al., 2015)	cCSC with secondary MNV	Retrospective non-comparative study	58	Bevacizumab (1.25 mg), ranibizumab (0.5 mg), or aflibercept (2 mg) Mean number of anti-VEGF injections: 4.45	46 eyes (43 patients)	38	Not mentioned	Mean LogMAR BCVA increased from 0.59 to 0.48.
(Jung et al., 2019a)	Pachychoroid neovasculopathy	Retrospective comparative study	64	3 monthly injections of ranibizumab (0.5 mg) or aflibercept (2 mg)	54 eyes (52 patients)	3	83% (aflibercept), 52% (ranibizumab) Complete SRF resolution was achieved after switching from ranibizumab to aflibercept in 13 of 15 eyes (86.7%)	The mean SFCT decreased significantly more in the aflibercept group than in the ranibizumab group (−35 μm vs. −9 μm). Mean LogMAR BCVA improved from 0.30 at baseline to 0.19 at 3 months in the aflibercept group and from 0.24 to 0.15 in the observation group.
(Lai et al., 2018)	Idiopathic MNV, CSC, angioid streaks, post-inflammatory retinochoroidopathy	Randomized controlled trial	54	Ranibizumab (0.5 mg) or placebo	119 eyes (119 patients in ranibizumab group), 59 eyes (59 patients in placebo group)	12	67% (ranibizumab), 74% (placebo)	Ranibizumab showed superior efficacy versus placebo at 2 months in terms of BCVA: +9.5 vs. +20.4 letters. Mean BCVA change at 12 months was +11.0 letters (ranibizumab) and +9.3 letters (placebo).
(Lejoyeux et al., 2021)	cCSC (90%), recurrent CSC, and aCSC	Retrospective noncomparative study	60	Either ranibizumab (0.5 mg) or aflibercept (2 mg) Mean number of anti-VEGF injections: 2.7	40 eyes (40 patients)	3	55%	Mean LogMAR BCVA increased from 0.46 to 0.38. SFCT decreased from 367 to 351 μm.

(Peiretti et al., 2018)	cCSC with MNV	Retrospective comparative study	59	Either full-fluence PDT or bevacizumab (1.25 mg), ranibizumab (0.5 mg), or pegaptanib (0.3 mg) Mean number of anti-VEGF injections: 3.44	16 eyes (16 patients in PDT group), 18 eyes (18 patients in anti-VEGF group)	12	Not mentioned	Mean LogMAR BCVA improved from 0.30 at baseline to 0.20 at 12 months, and no significant changes in BCVA were seen between the PDT and the anti-VEGF group.
(Romdhane et al., 2020)	CSC (all types)	Retrospective study	64	Ranibizumab (0.5 mg) or aflibercept (2 mg) on a monthly as-needed regimen. 22 eyes (81%) aflibercept and ranibizumab in 5 eyes (19%) Mean number of anti-VEGF injections: 2.8	27 eyes (25 patients)	3.4 (mean)	45%	Mean LogMAR BCVA improved from 0.25 at baseline to 0.21 after treatment.
(Roy et al., 2017)	CSC with MNV	Retrospective case series	43	Either bevacizumab (1.25 mg) or ranibizumab (0.5 mg)	10 eyes (9 patients)	28 (mean)	60%	Mean LogMAR BCVA improved from 0.62 to 0.47.
(Sacconi et al., 2019)	cCSC complicated by MNV	Retrospective study	53	Either half-fluence PDT or single-dose aflibercept (2.0 mg) injection	30 eyes (26 patients)	1	Not mentioned	Mean LogMAR BCVA improved from 0.24 at baseline to 0.18 at 1 month after the treatment in the PDT group, compared to 0.35 and 0.24, respectively in the aflibercept group. The MNV area decreased from 0.586 mm^2 to 0.553 mm^2 in the PDT group, and from 0.767 mm^2 to 0.733 mm^2 in the aflibercept group.
(Schworm et al., 2020)	cCSC	Retrospective study	65	6 intravitreal injections with ranibizumab (0.5 mg) or aflibercept (2 mg) ever 4 weeks	21 eyes (21 patients)	6	43% (ranibizumab group), 71% (aflibercept group)	Mean LogMAR BCVA improved from 0.65 to 0.49.
(Song et al., 2021)	cCSC patients with and without MNV	Retrospective case series	51 (with MNV)	1 intravitreal injection with bevacizumab (1.25 mg)	31 eyes (31 patient with MNV)	1	Not reported	Mean LogMAR BCVA increased from 0.31 to 0.24.

aCSC, acute central serous chorioretinopathy; BCVA, best-corrected visual acuity; cCSC; chronic central serous chorioretinopathy; MNV, macular neovascularization; ETDRS, Early Treatment of Diabetic Retinopathy Study; FA, fluorescein angiography; LogMAR, logarithm of the minimal angle of resolution; OCT, optical coherence tomography; PDT, photodynamic therapy; SFCT, subfoveal choroidal thickness; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

3.2.2 Severe chronic CSC

Severe cCSC should be considered in patients who present with at least one of the following clinical findings: a cumulative area of at least 5 optic disc diameters of diffuse atrophic RPE alterations visualized on mid-phase FA; at least two leakage points separated by at least 1 disc diameter of non-hyperfluorescent healthy-appearing retina on mid-phase FA; an area of diffuse fluorescein leakage of >1 optic disc diameter on mid-phase FA, with no evident focal leakage (diffuse leakage); and/or the presence of posterior cystoid retinal degeneration (PCRD) on OCT (Mohabati et al., 2018b).

Treatment should be recommended for patients with cCSC complicated by PCRD, due to the likelihood of progressing to severe vision loss (Mohabati et al., 2020b; Piccolino et al., 2008); unfortunately, however, both half-dose PDT and standard PDT have relatively low efficacy in this patient group (Cardillo Piccolino et al., 2003; Nicolo et al., 2012). A study by Mohabati and colleagues that included 25 eyes with severe cCSC with PCRD treated with various reduced-setting PDT protocols found that 11 eyes (44%) achieved complete resolution of PCRD, 12 eyes (48%) showed a reduction in PCRD after treatment, and the remaining 2 eyes (8%) had no change at the first post-treatment visit (Mohabati et al., 2018b). In contrast, a previous study by Silva and colleagues found that the intraretinal fluid was completely resolved in all 10 patients with cCSC with PCRD following treatment with full-setting PDT (Silva et al., 2013). The relatively poor response to PDT may be explained in part by the degenerative nature of PCRD in cCSC, in which factors other than persistent SRF and choroidal and RPE dysfunction become relevant once PCRD reaches the chronic phase. The contrasting results obtained using PDT for the treatment of cCSC with PCRD may also be due to the concurrent presence of diffuse atrophic RPE alterations, which can pose a challenge when selecting the area for laser treatment. In addition, intraretinal fluid may be reabsorbed more slowly than SRF (Cardillo Piccolino, 2010; Mohabati et al., 2018b). The location of cystoid intraretinal spaces and chorioretinal adherence has also been linked to sites of subretinal atrophy and fibrosis (Cardillo Piccolino et al., 2008; Piccolino et al., 2008). In eyes with severe cCSC, subretinal fibrotic scars can also develop after the appearance of subretinal fibrin (Schatz et al., 1995), and these scars may represent focal areas of chorioretinal adherence and breakdown of the RPE barrier, which provide a direct passage for fluid to diffuse from the choroid into the retina in the case of choroidal hyperperfusion (Cardillo Piccolino et al., 2008; Piccolino et al., 2008).

The possibility of MNV in cCSC with intraretinal fluid should be ruled out by performing OCT, OCT-A, FA, and/or ICGA, as MNV can be present in up to 45% of severe cCSC cases and should be treated accordingly (Sahoo et al., 2019) (see section 3.2.1).

3.3 Atypical CSC

In some cases, it can be difficult to classify CSC as aCSC, cCSC, or severe cCSC, particularly given the wide variability in how these subtypes are defined (Singh et al., 2019). Atypical CSC is defined as

CSC with atypical features such as the bullous variant with an exudative retinal detachment with shifting fluid, the presence of a RPE tear, or an association with other retinal diseases. In addition, conclusively diagnosing an associated MNV in CSC can be difficult, although this can be facilitated by the presence of FIPED with underlying mid-to-hyperreflective material (presumed to be neovascular tissue; see Fig. 6) and/or the presence of neovascular tissue on OCT-A (Guo et al., 2021a; Hagag et al., 2021). International multicenter groups are currently attempting to develop a more comprehensive, uniform, and practical consensus-based classification, although this is challenging, particularly given the broad and variable phenotypic range of CSC (Chhablani et al., 2022; Chhablani et al., 2020). In cases in which the diagnosis is unclear, it can be difficult to determine the optimal treatment strategy, which can depend heavily on factors other than the CSC subtype, including the patient's wishes, age, visual symptoms, the physician's preference, disease progression, and a variety of other clinical and non-clinical parameters. Thus, the broad range of differential diagnoses for macular SRF should be considered (van Dijk and Boon, 2021).

3.4 What to do in the event of persistent SRF

The treatment options for patients with CSC whose SRF does not respond to the initial treatment remain poorly understood. However, several options should be considered, including repeat treatment, applying a different treatment, and/or re-evaluating the original diagnosis of CSC.

In patients with CSC who have persistent SRF after receiving a treatment other than reduced-setting PDT, a different treatment approach can be used. Two randomized controlled crossover trials have shown that half-dose PDT can still be a highly effective treatment for cCSC despite previous failed treatments using other treatment options (Feenstra et al., 2022c; van Rijssen et al., 2020b). For example, the REPLACE trial found that crossover treatment with half-dose PDT after prior failure (defined as persistent SRF) of primary treatment with HSML led to complete SRF resolution 1 year after PDT treatment in 78% of patients (van Rijssen et al., 2020b). Similarly, the recent SPECS trial found that crossover treatment with half-dose PDT after unsuccessful treatment with eplerenone induced relatively rapid and complete SRF resolution in 87% of patients at 3 months, along with an improvement in foveal sensitivity on microperimetry (Feenstra et al., 2022c).

In patients who do not respond to reduced-setting PDT, the initial diagnosis of CSC should be re-evaluated (van Dijk and Boon, 2021), even when the diagnosis was based on multimodal imaging that included FA, ICGA, and OCT-A. Because CSC is part of a broad differential diagnosis, establishing the correct diagnosis is often challenging (van Dijk and Boon, 2021). In addition, CSC can be complicated by the presence of MNV, which can develop during follow-up and may require treatment with intravitreal anti-VEGF injections, in addition to half-dose PDT.

When a repeated series of multimodal imaging still shows findings that are characteristic of CSC, patients with persistent or recurrent SRF who were previously treated with reduced-setting PDT can be re-treated with reduced-setting PDT, particularly when the FA and/or ICGA findings show persistent leakage that may respond to re-treatment. Moreover, the relatively new technique ultra-widefield ICGA may reveal choroidal alterations outside the central 55° area covered by traditional imaging, which could have implications for treatment efficacy.

4. Future perspectives

In recent years, a strong foundation for establishing an evidence-based treatment strategy for CSC has been established, thanks largely to the availability of the results obtained from the PLACE, VICI, and SPECTRA trials. Currently, half-dose PDT appears to be the favored treatment in CSC. However, because CSC is a complex disease, future RCTs are needed in order to optimize treatment.

Even though the treatment effects of half-dose PDT and placebo were compared indirectly in a meta-analysis, no large RCT has been performed to directly compare half-dose PDT versus placebo (van Dijk et al., 2022b). The upcoming PAINT (photodynamic laser therapy with verteporfin versus placebo for chronic central serous chorioretinopathy) RCT will be the first large, randomized, double-masked, controlled trial to compare half-dose PDT and placebo in patients with cCSC. Half-dose PDT is currently the only treatment that shows any significant benefits with respect to the treatment of cCSC, yet some countries feel that the current level of evidence is not adequate to justify covering this procedure. Therefore, this new RCT may provide valuable new evidence to support the use of half-dose PDT for treating CSC and may address questions regarding natural fluctuations in the disease course. Unfortunately, however, the PAINT RCT is currently on hold due to the recent shortage of verteporfin, the photosensitized dye used to perform PDT.

Despite the promising results obtained in various RCTs using half-dose PDT for the treatment of CSC, it should be noted that this treatment does not work in all CSC cases. Therefore, other treatment options for CSC should still be investigated. The aforementioned global shortage of verteporfin further illustrates the need for additional treatment options and/or the development of new photosensitized agents other than verteporfin (Sirks et al., 2022).

In the future, it may be possible to further optimize the treatment of CSC by developing a "personalized medicine" treatment strategy, which may also predict the likelihood of success. This strategy could include the individual patient's clinical characteristics, findings on multimodal imaging, and possibly even the patient's genetic profile (Feenstra et al., 2022a). In addition, developing a more accurate, validated multimodal imaging–based classification of CSC subtypes may also help to develop an optimal treatment strategy for each CSC subtype. Furthermore, the introduction of artificial intelligence (AI)–based and deep learning (DL)–based strategies may play a valuable role in improving the diagnosis, follow-up, and decision-making process in CSC (Aoyama et al., 2021; Pfau et al., 2021). Moreover, additional studies are needed in order to develop the ideal treatment strategy for cases that present with both intraretinal fluid (e.g., PCRD) and SRF. Finally, long-term follow-up is needed in order to determine the maximum number of PDT treatments that be safely performed while still achieve complete SRF resolution, as well as further information regarding the role of PDT in preventing recurrence.

5. Conclusions

Recently, data from several large RCTs involving patients with CSC become available, providing a wealth of new information regarding the treatment of this disease. For example, treatment of aCSC can often be deferred for up to 3-4 months after diagnosis, but early treatment should be considered for patients who rely heavily on optimal vision for professional reasons, and to reduce the risk of recurrence. When treatment for aCSC is indicated, half-dose PDT is currently the treatment of choice for achieving rapid SRF resolution, a faster improvement in BCVA, and a decreased risk of recurrence compared to other available treatments. Based on the data of the recently reported RCTs, half-dose PDT should also be considered the treatment of choice for cCSC. Importantly, the current body of evidence implicating half-dose PDT as the treatment of choice in cCSC may support coverage of this off-label use. In elderly patients, a flat-irregular PED is highly suggestive of MNV, which can be confirmed using multimodal imaging such as OCT-A and ICGA. In addition, ICGA can be used to detect a polypoidal component. Based on current evidence, CSC with MNV should be treated with half-dose PDT and/or intravitreal injections of anti-VEGF medication.

In 2021 and 2022, a global shortage of verteporfin significantly affected the ability to treat a wide range of ocular diseases, including CSC. Given the current paucity of evidence supporting the efficacy of other treatment options for CSC—aside from the treatment of extramacular leakages sites using focal laser treatment—new targets and modes of action should be identified. In addition, novel treatment strategies are needed, as well as well-designed clinical trials and efforts to prevent future shortages of verteporfin.

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FIGURE LEGENDS

Figure 1: Multimodal imaging of a 34-year-old man diagnosed with acute central serous chorioretinopathy (aCSC).

The presence of foveal subretinal fluid overlying a thick (526 μm) choroid with pachyvessels (white arrows) can be seen on optical coherence tomography (OCT, A). Fluorescein angiography shows a focal area of hyperfluorescent dye leakage that increases and ascends into the subretinal space to produce a "smokestack" leakage pattern with additional hyperfluorescent areas of choroidal vascular hyperpermeability (white arrows, B, D, F). Indocyanine green angiography shows a similar leakage pattern with additional hyperfluorescent areas of choroidal vascular hyperpermeability (C, E, G). The serous detachment seen on OCT (A) and color fundus photography (H) has a hyperautofluorescent border with mild central hypo-autofluorescence visible on fundus autofluorescence (I).

Figure 2: Multimodal imaging of a 57-year-old man with chronic central serous chorioretinopathy (cCSC).

Subretinal fluid and choroidal thickening are visible on optical coherence tomography (A). Two focal areas of hyperfluorescent leakage (white arrows) and retinal pigment epithelial detachment (black arrows) are seen at 1 min (B), 3 min (D), and 6 min (F) during fluorescein angiography. Choroidal vascular hyperpermeability is visible on indocyanine green angiography at 6 min (C), 10 min (E), and 20 min (G). Color fundus photography shows pigmentary abnormalities (H). Fundus autofluorescence (I) shows mostly hyperautofluorescent abnormalities, including an area corresponding to a descending tract of retinal changes due to chronic subretinal fluid leakage following gravity(white arrow) as well as an area corresponding to the presence of subretinal fluid accumulation (black arrow).

Figure 3: Two cases of central serous chorioretinopathy (CSC) complicated by subretinal hyperreflective material and posterior cystoid retinal degeneration.

(A-D) Multimodal imaging of a 32-year-old man with acute central serous chorioretinopathy. Fundus photography (A) shows the presence of yellow-white subretinal material, possibly fibrin, which is hyperreflective on optical coherence tomography (OCT; D) and hyperautofluorescent on fundus autofluorescence (C), with a roughly vertical sausage-shaped clear area (arrow in A) corresponding to a small round hyporeflective zone on OCT (arrow in D). This clear zone within the lesions on fundoscopy and the hyporeflective zone on OCT likely correspond to the upward leakage track originating from the focal leakage point on fluorescein angiography (right arrow in B). In addition,

some mildly atrophic retinal pigment epithelial changes in the temporal macula (left arrow in B) also indicate a certain degree of advanced or chronic disease.

(E-I) Multimodal imaging of a 72-year-old man with severe chronic central serous chorioretinopathy with posterior cystoid retinal degeneration. Multiple areas of leakage are visible on fluorescein angiography at 3 min (F), along with hyperfluorescent changes with an indistinct border on indocyanine green angiography at 10 min, characteristic of diseases that are part of the pachychoroid disease spectrum (G). Fundus autofluorescence imaging shows hyperautofluorescent and hypo-autofluorescent areas (E). Posterior cystoid retinal degeneration (PCRD) is visible on the foveal OCT scan (arrow in I). Note that the FA leakage does not cover the entire extent of the PCRD lesion (H), allowing for the differentiation between PCRD and choroidal neovascularization–associated intraretinal edema.

Figure 4: Three cases of CSC treated with half-dose photodynamic therapy (PDT).

(A-J) Multimodal imaging of a 31-year-old man with aCSC. Optical coherence tomography (OCT) shows subretinal fluid (SRF) that includes the fovea (A). Fluorescein angiography (FA) shows focal leakage (arrow) that increases over time; images are shown at 1 min (B), 3 min (D), and 6 min (F). Indocyanine-green angiography (ICGA) at 6 min (C), 10 min (E), and 15 min (G) shows limited hyperfluorescence at the area of focal leakage. The area to be treated with PDT is demarcated by the circle shown in the ICGA image taken at 10 min (E). Fundus photography shows retinal pigment epithelium (RPE) alterations (H). Fundus autofluorescence imaging (FAF) shows hyperautofluorescence at the fovea and at the site of leakage (I). SRF is absent on OCT 2 months after half-dose photodynamic therapy (PDT) (J).

(K-T) Multimodal imaging of a 52-year-old man with cCSC. On OCT (K), SRF is present, in addition to debris within the SRF accumulation (arrow). FA shows three focal leakage points (arrows), which increase in size at 1 min (L), 3 min (M), and 6 min (P), with extensive hyperfluorescence on ICGA at 6 min (M), 10 min (O), and 15 min (Q). The area to be treated with PDT is demarcated by the circle shown in the ICGA image taken at 10 min (O). Fundus photography shows RPE abnormalities (R). FAF shows extensive hyperautofluorescence (S). SRF is absent on OCT 3 months after half-dose PDT (T).

(U-DD) Multimodal imaging of a 47-year-old man with cCSC. OCT (U) shows SRF and an RPE detachment (arrow). On FA, the macular pigment epithelial detachment and areas of focal leakage (white arrows) are visible at 1 min (V), 3 min (X), and 6 min (Z); the RPE detachment is also visible on FA (black arrows). An additional focal leakage point nasal to the optic nerve is also visible on FA.

During half-dose PDT, both the macular and nasal leakages points can be treated, using two separate treatment spots indicated in (Y). ICGA shows extensive hyperfluorescent changes at 4 min (W), 10 min (Y), and 20 min (AA). Fundus photography (BB) shows RPE abnormalities, and FAF (CC) shows hyperautofluorescent and hypo-autofluorescent abnormalities. SRF is absent on OCT 2 months after half-dose PDT (DD).

Figure 5: Multimodal imaging of a 49-year-old man with cCSC.

Optical coherence tomography (A) shows subretinal fluid (arrow). On fluorescein angiography at 6 min (B), a focal leakage point is visible (arrow). Mid-phase (10 min after injection) indocyanine-green angiography (ICGA) shows hyperfluorescent areas (arrow) (C); the fovea is indicated by the white circle. (D) The same ICGA image is shown in (C), with the area to be treated with half-dose photodynamic therapy indicated by the black circle. (E) The same ICGA image is shown in (C), with the area to be treated with high-density subthreshold micropulse laser (HSML) indicated by the pattern of small black circles (the pattern of closely spaced laser spots for HSML is shown larger than the actual spot size for illustrative purposes only).

Figure 6: Multimodal imaging of a 55-year-old man with cCSC complicated by a type 1 macular neovascularization.

Foveal subretinal fluid and a relatively flat, irregular retinal pigment epithelial detachment (FIPED) are visible on optical coherence tomography (arrow) (OCT; A) and are accompanied by retinal pigment epithelium alterations on fundus photography (B). The space below the FIPED and above Bruch’s membrane shows some grayish reflectivity, which is indicative of neovascular tissue. Leakage of fluorescein and diffuse retinal pigment epithelium alterations are visible on mid-phase (arrow) (C) and late-phase (D) fluorescein angiography. Indocyanine green angiography shows large hyperfluorescent areas with an indistinct border suggestive of choroidal hyperpermeability as seen mid-phase (F) and late-phase (G) photos, and a smaller neovascular membrane (delineated by the arrows in F and G). A neovascular network is clearly visible when segmentation is adjusted to cover the space between the retinal pigment epithelium and Bruch's membrane on OCT-A (E).

Figure 7: Flowchart depicting the proposed evidence-based treatment strategy for acute central serous chorioretinopathy. Note: if the patient is currently taking corticosteroids, discuss stopping their use prior to treatment.

[1] Treat hyperfluorescent areas on indocyanine green angiography (ICGA) that correspond to the area of (focal) leakage on fluorescein angiography (FA) and subretinal fluid on optical coherence tomography (OCT). In case of multiple areas with focal leakage, a large spot including all areas can be used, or multifocal immediately sequential spots may be used, starting with the area including the fovea (if fovea is involved).

[2] In case of only a small amount of residual subretinal fluid (SRF), a conservative approach may be followed, with a follow-up visit including OCT imaging after 1–3 months to see if SRF eventually resolves completely. In case of persistent/increased SRF at that stage, the downstream treatment decision pathway may be followed.

[3] Half-dose or half-fluence photodynamic therapy (PDT) may be added in order to treat the choroidal dysfunction/pachychoroid factor of the disease, but limited data are available to support this combined treatment. When a neovascular component of polypoidal choroidal vasculopathy (aneurysmal type 1 neovascularization) is present, PDT (either full-dose, half-dose, or half-fluence) can also be added to anti-vascular endothelial growth factor treatment.

[4] Another half-dose or half-fluence PDT can be performed, but full-dose with full-fluence PDT may also be considered.

Abbreviations: MNV, macular neovascularization; CSC, central serous chorioretinopathy; FA, fluorescein angiography; FAF, fundus autofluorescence; ICGA, indocyanine green angiography; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; PDT, photodynamic therapy; RPE, retinal pigment epithelium; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

Figure 8: Flowchart depicting of the proposed evidence-based treatment strategy for chronic central serous chorioretinopathy. Note: if the patient is currently taking corticosteroids, discuss stopping their use prior to treatment.

[1] Treat hyperfluorescent areas on indocyanine green angiography (ICGA) that correspond to the area of (focal) leakage on fluorescein angiography (FA) and subretinal fluid on optical coherence tomography (OCT). In case of multiple areas with focal leakage, a large spot including all areas can be used, or multifocal immediate sequential spots may be used, starting with the area including the fovea (if fovea is involved).

[2] In case of only a small amount of residual subretinal fluid (SRF), a conservative approach may be followed, with a follow-up visit including OCT imaging after 1–3 months to see if SRF eventually

resolves completely. In case of persistent/increased SRF at that stage, the downstream treatment decision pathway may be followed.

[3] Half-dose or half-fluence photodynamic therapy (PDT) may be added in order to treat the choroidal dysfunction/pachychoroid factor of the disease, but limited data are available to support this combined treatment. When a neovascular component of polypoidal choroidal vasculopathy (aneurysmal type 1 neovascularization) is present, PDT (either full-dose, half-dose, or half-fluence) can also be added to anti-vascular endothelial growth factor treatment.

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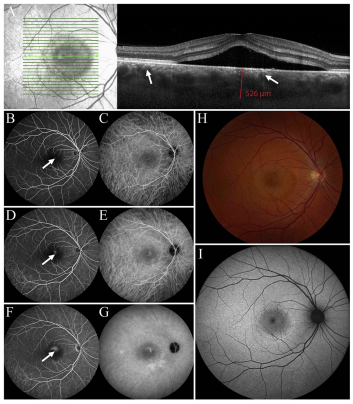
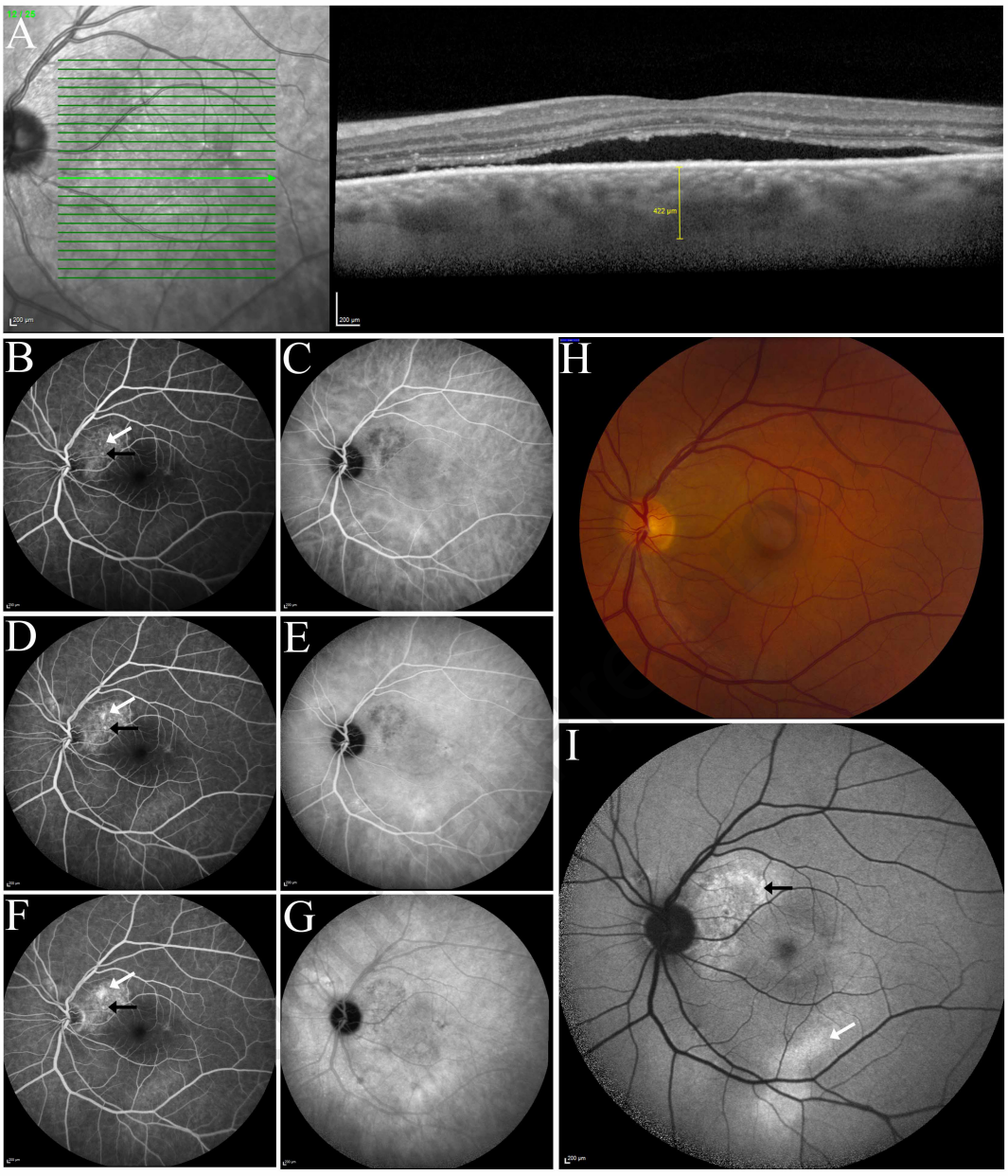
Abbreviations: MNV, macular neovascularization; CSC, central serous chorioretinopathy; FA, fluorescein angiography; FAF, fundus autofluorescence; ICGA, indocyanine green angiography; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; PDT, photodynamic therapy; RPE, retinal pigment epithelium; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

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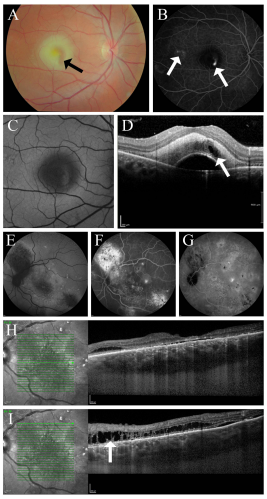

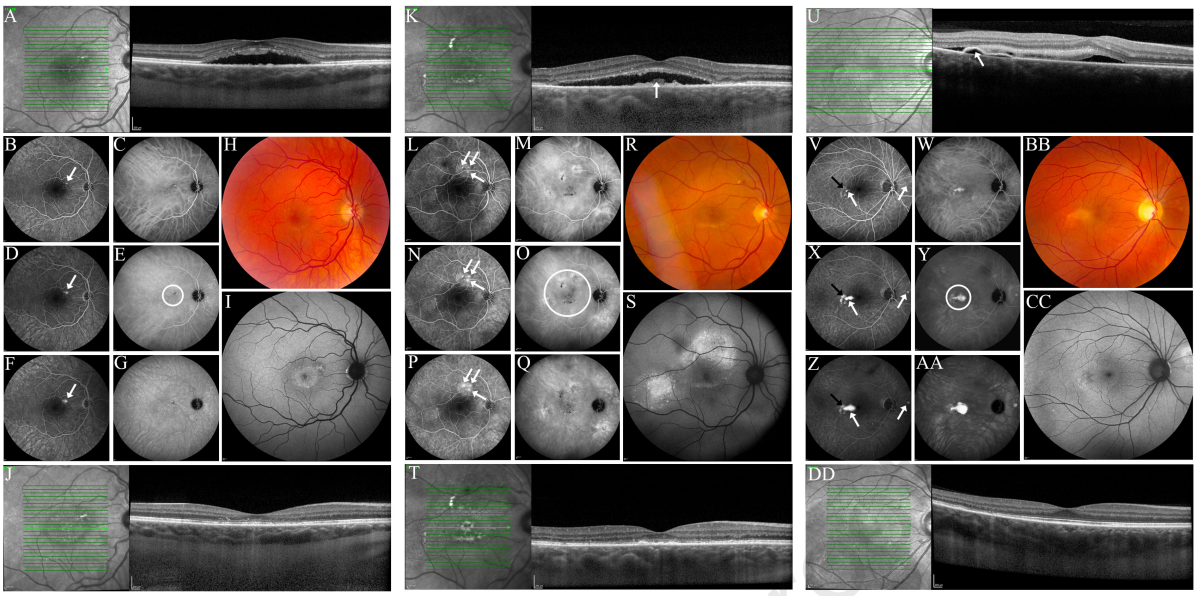

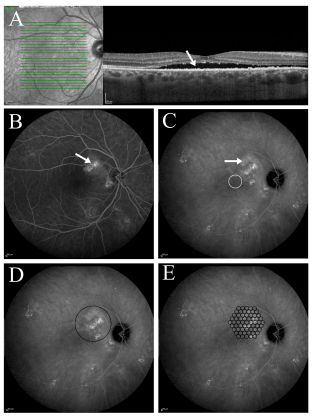

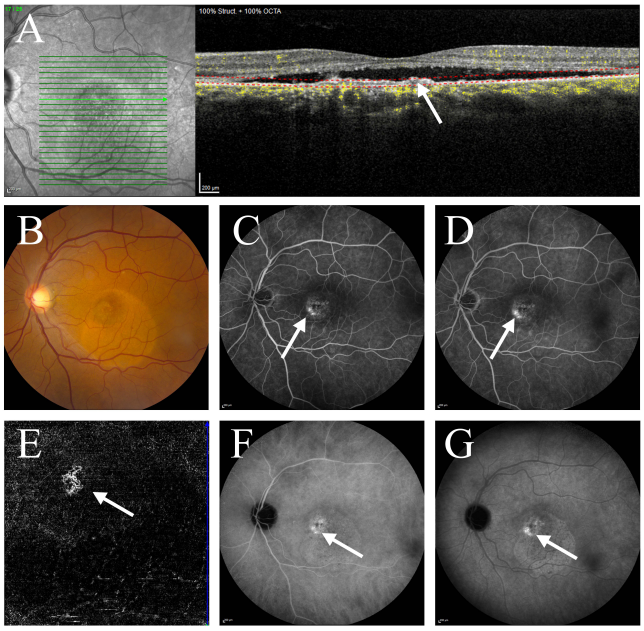

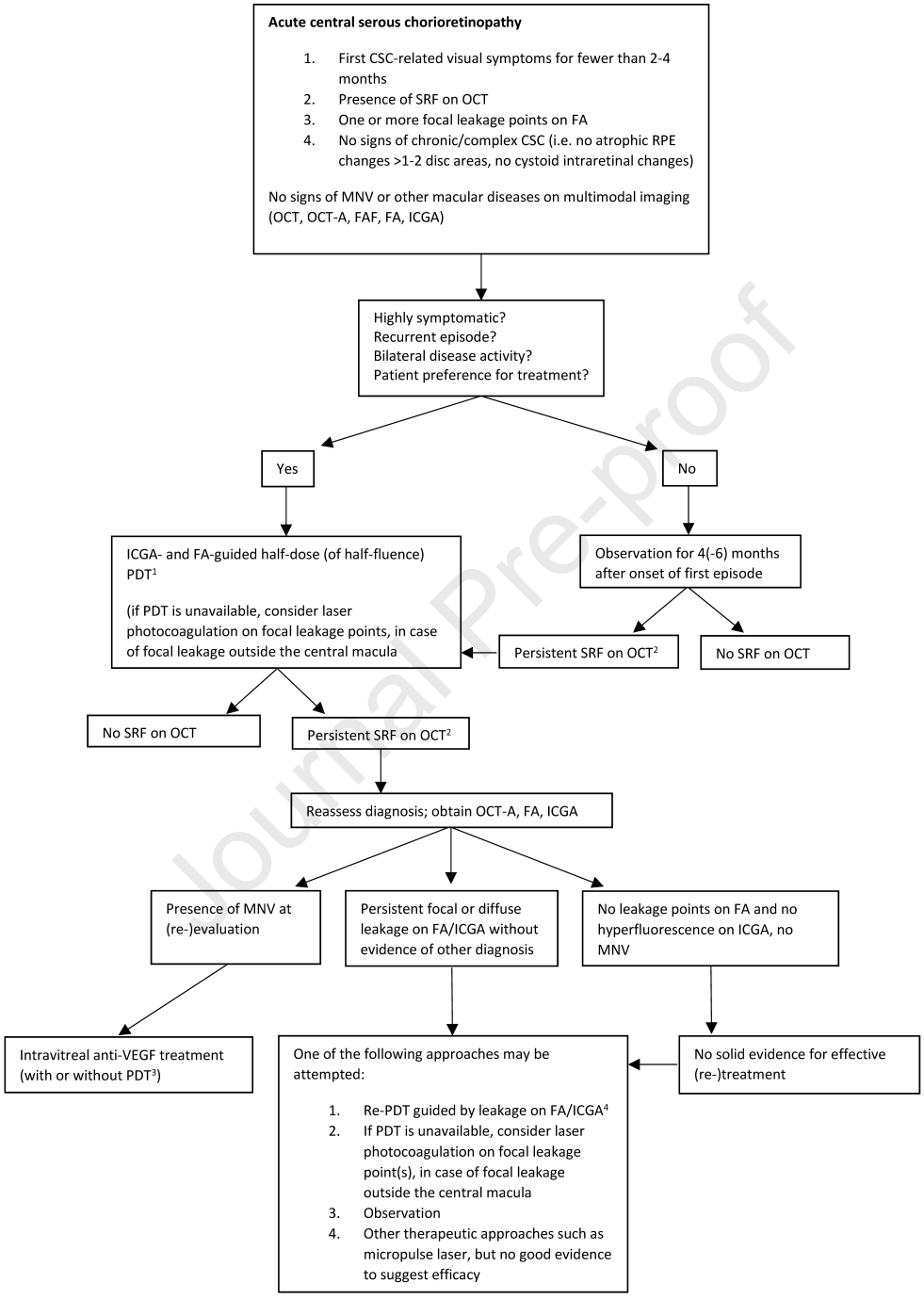

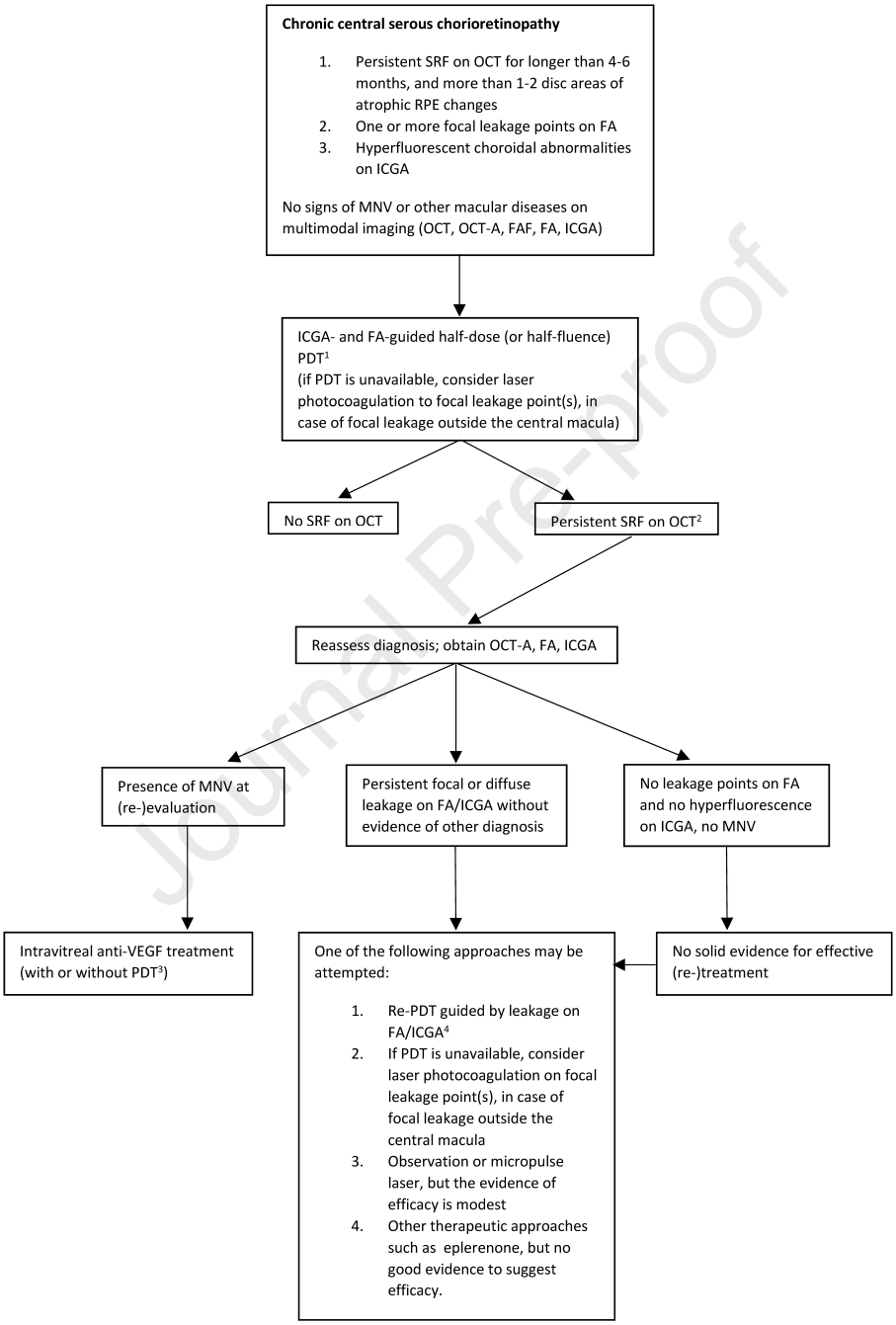

Highlights

- Controversy on the treatment of central serous chorioretinopathy (CSC) remains
- In chronic CSC, half-dose (or half-fluence) photodynamic therapy (PDT) is best supported by currently available evidence
- In acute CSC, observation or early half-dose (or half-fluence) PDT is recommended
- PDT efficacy is likely associated with targeting of the dysfunctional choroid
- Non-central leaks in chronic CSC may be treated with laser photocoagulation

Key words

Central serous chorioretinopathy; Treatment Guideline; Photodynamic therapy; Micropulse laser; Mineralocorticoid receptor antagonist

Contents