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REVIEW

What is new in central serous chorioretinopathy?

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Abstract

Central serous chorioretinopathy (CSCR) is considered a benign, self-limiting disease. However, as many as third of the patients have recurrent episodes or chronic disease that may cause significant functional impairment. New diagnostic tools and new treatment modalities are emerging in order to improve the functional outcomes of these patients. Spectral domain optical coherence tomography (SD-OCT) has the ability to image individual layers of the retina and choroid. SD-OCT images in CSCR patients have demonstrated increased subfoveal thickness measurements, high reflective deposits in areas of subretinal precipitates and changes in the Retinal pigment epithelium layers of the asymptomatic eyes of patients with supposedly unilateral CSCR. A positive correlation was found between the level of distribution to the layer of inner segment/outer segment junction of the photoreceptors and the visual impairment. Fundus autoflouresence images show a wide variety during different stages of the disease in CSCR patients. Minimal abnormalities during the early stages are followed by hyperautofluoresence in the detached area in later stages, often in a manner of inferior gravitation and at the borders of the detachments. The chronic phase is characterized by varying degrees of atrophy and areas of decreased autofluorescence surrounding areas of chronic leaks. These changes help differentiate an active disease from an inactive state. Multifocal electroretinography (mfERG) has the ability to demonstrate a persistent depression despite the resolution of subretinal detachments. It is therefore being investigated as a follow up tool for patients with chronic CSCR. An excellent correlation was found between changes in mfERG and visual function. Macular microperimetry, measuring retinal sensitivity within the central visual field, is intended to compensate for the underestimation of visual impairment in patients with macular diseases. Reduced retinal sensitivity was found in areas of previous subretinal fluids in CSCR patients. The device can also serve as a follow up tool in these patients. Regarding treatment in CSCR patients, focal argon laser photocoagulation treatment may be applied to small extrafoveal leaks. However, the main purpose of this treatment is to shorten disease duration, with no advantage over observation regarding final visual outcome, rate of progression to chronic CSCR or number of recurrences. Photodynamic therapy (PDT) with verteporfin has been shown to completely resolve serous detachment in 60%-80% of patients and to have a partial affect in the remaining patients. Reduced-fluence treatment is replacing full-fluence therapy in order to minimize side effects with no accompanying reduced effectiveness. Visual acuity is also improved following reduced-fluence PDT compared to placebo. It has also been found that patients with intense hyperfluorescence are more likely to show resolution of accumulating fluid compared to patients with mild or no leakage observed on indocyanine-green angiography prior to treatment. Regarding newer treatment modalities, intravitreal injections of anti-vascular endothelial growth factor agents have a limited effect in patients with CSCR. Recent reports have not demonstrated an advantage for this treatment in regards to anatomic and functional outcome. Micropulse diode laser was not proven to be safer or more effective than argon laser or PDT. Corticosteroid antagonists, not tested in controlled trials, may have a beneficial effect in patients with CSCR. Aspirin may also play a role in treating these patients, with rapid recovery of visual acuity and reduced number of recurrences observed. In

conclusion, imaging is evolving rapidly while the clinical implications of these new imaging modalities are less clear. Large randomized trials investigating different treatment modalities are still lacking.

Key words: Central serous chorioretinopathy; Optical coherence tomography; Fundus autoflouresence; Multifocal electroretinography; Macular microperimetry

Core tip: (1) New diagnostic tools and therapies may improve the prognosis of patients with chronic or recurrent central serous chorioretinopathy; (2) Changes in fundus autoflouresence images help differentiate an active disease from an inactive state; (3) Multifocal electroretinography and macular microperimetry may serve as follow up tools due to their ability to measure macular visual function; (4) Focal argon laser photocoagulation shortens disease duration but does not affect final prognosis; (5) Reduced-fluence photodynamic therapy improves visual acuity and resolves serous detachments; and (6) The role of anti-vascular endothelial growth factor agents, micropulse diode laser, corticosteroid antagonists, aspirin, anti-viral or Helicobacter pylori treatment is still being investigated.

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INTRODUCTION

Central serous chorioretinopathy (CSCR) was first described by Albrecht von Graefe in 1866 as a relapsing central luetic retinitis[1]. The various terms later used to describe the disease, including the current acceptable term CSCR first used by Gass[2] in 1967, have omitted the relapsing characteristic from the term. However, relapsing serous detachments of the neurosensory retina are known to occur in as many as third of the patients[3]. Moreover, the recurrent and chronic nature of CSCR may result in severe and irreversible visual loss in these patients[4]. Therefore, in order to improve patients outcome, there is an ongoing search for new diagnostic tools, shedding more light on disease pathophysiology, and for new treatments and different treatment protocols.

PATHOPHYSIOLOGY

The typical presentation of CSCR is serous detachment of the neurosensory retina, but the source of the accumulating subretinal fluid is still not completely understood[2-13]. Retinal pigment epithelium (RPE) dysfunction has been hypothesized as the primary pathologic mechanism in CSCR, in part due to images obtained using fluorescein angiography (FA)[4-6]. These images show characteristic single or multiple leaks from the RPE, implicating the RPE as a major factor in the pathophysiology, as can be seen in Figure 1. However, different investigative tools led investigators to challenge this hypothesis. According to some reports, the choroid seems to be primarily affected, with the retinal changes seen with FA representing a later stage in the mechanism of the disease progression[7].

In order to further understand the role of the choroid in the disease, indocyanine-green angiography (ICGA) images were investigated. The congestion and dilatation of choroidal capillaries and veins, the choroidal staining and the leakage into the interstitial space all prove the choroid plays a major role in the accumulation of fluid in CSCR[12,13]. These changes in ICGA images are demonstrated in Figure 2. However, ICGA was found to have some limitations as a tool for diagnosis and follow up of patients. Previous studies on cross-sectional optical coherence tomography (OCT) images of eyes with chronic CSCR reported increased choroidal thickness observed, with no corresponding hyperflouresence observed on ICGA[14]. Moreover, ICGA gives a 2-dimensional scans, which means that all choroidal layers overlap in the angiogram.

NEW INSIGHTS ON PATHOPHYSIOLOGY FROM NEW IMAGING AND EXAMINATION MODALITIES

Spectral domain optical coherence tomography

The introduction of spectral domain optical coherence tomography (SD-OCT) as a more accurate imaging tool, with its ability to characterize individual layers of the retina and choroid and its noninvasive characteristic, has led to important observations regarding CSCR. The subfoveal thickness was found to be increased by 50%-80% in CSCR patients compared to normal eyes in different reports, when measured by enhanced depth imaging OCT[14-17].

Another measurement that can be performed with SD-OCT is the thickness of the outer nuclear layer (ONL). In one study, ONL thickness was found to be correlated with visual acuity in patients with resolving CSCR[18]. In that study, the mean ONL thickness measured in patients with resolved CSC was 74.6 μm in patients with visual acuity worse than 20/20 compared to 103 μm in patients with visual acuity of 20/20 or better[18]. That same group of researchers also showed elongation of photoreceptors outer segments and decreased thickness of the outer nuclear layer in CSCR, as a possible sign for photoreceptors apoptosis[19].

SD-OCT has also shed some light on the multiple, dot-like, yellow precipitates and subretinal yellow material within the area of a serous retinal detachment in patients with CSCR. These deposits correlate with high reflective deposits on SD-OCT[20,21] (Figure 3). Different hypothesis regarding these substances has been proposed, including the accumulation of shed photoreceptor outer segments, fibrin or lipids, or macrophages clearing the subretinal

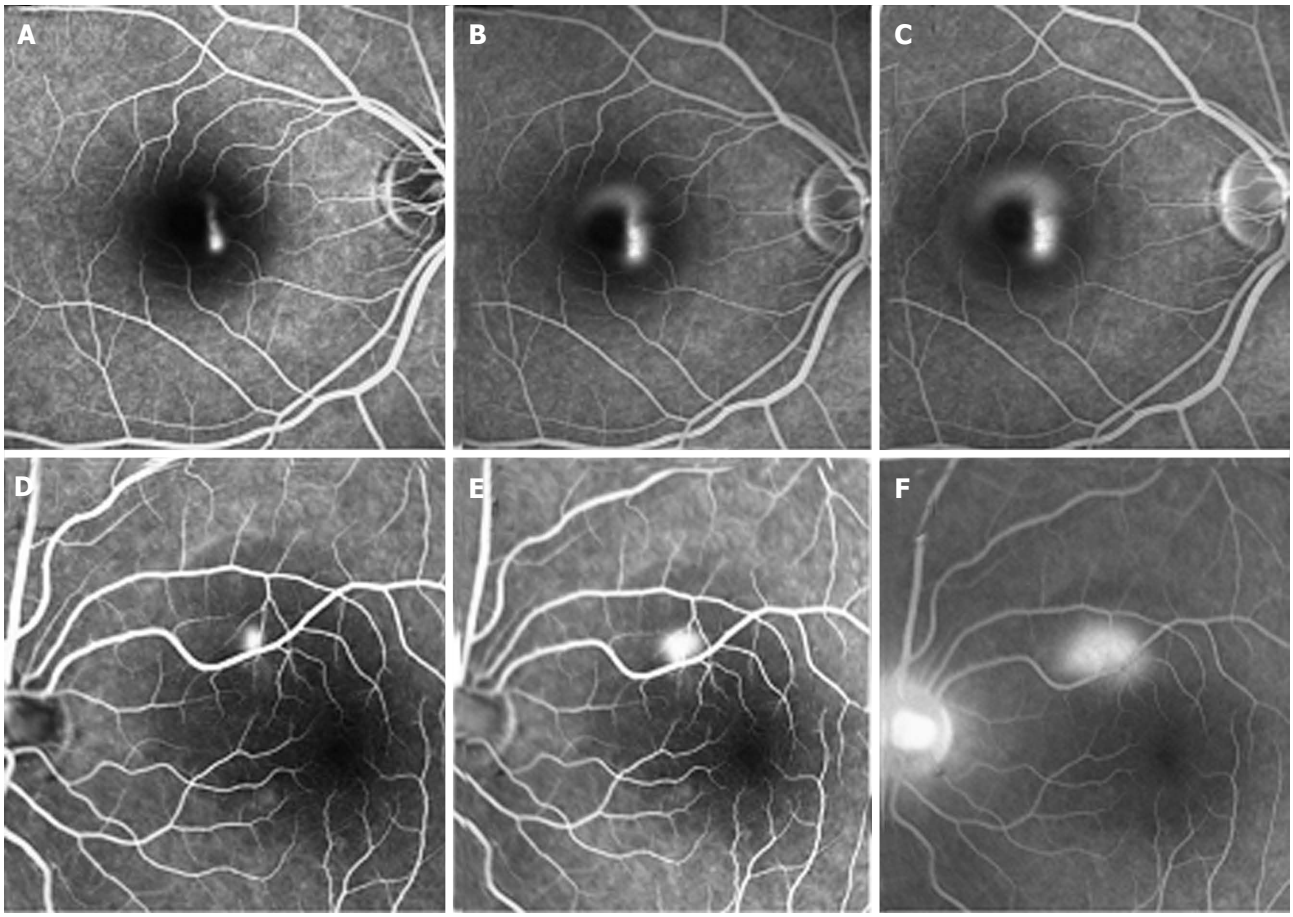

Figure 1 Two different patterns of hyperfluorescent dye leakage on fluorescein angiogram in acute central serous chorioretinopathy; Smokestack pattern of leakage (A, B and C) and inkblot pattern of dye leakage (D, E and F).

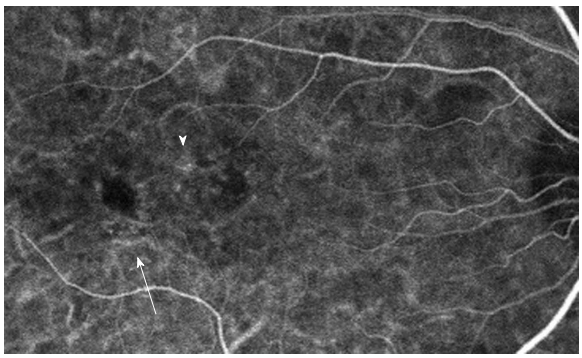

Figure 2 Indocyanine green angiography in a patient with chronic central serous chorioretinopathy. Note congestion and dilatation of choroidal capillaries and veins (arrow) and choroidal staining (arrowhead).

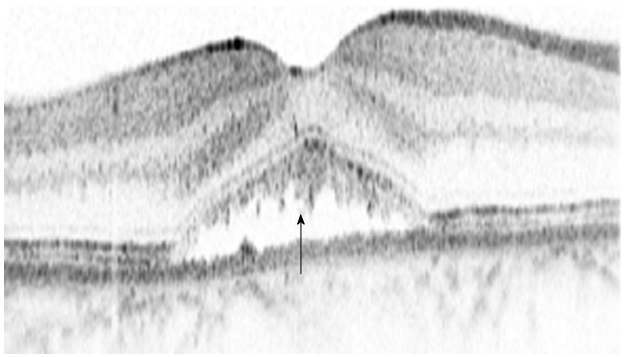

Figure 3 Spectral domain optical coherence tomography of acute central serous chorioretinopathy. Note high reflective subretinal deposits within the area of a serous retinal detachment (arrow).

space. However, the exact nature of these deposits and their origin is yet to be determined[21].

The bilateral nature of CSCR was also demonstrated by SD-OCT, even in eyes with supposedly unilateral disease[22]. Changes in the RPE cells layer has been previously shown in patients with CSCR, specifically around areas of a demonstrated leakage on FA[23]. This study investigated these RPE changes in the asymptomatic eyes of patients with CSCR in the other eye, using 3 dimensional single-layer RPE analyses. Presence of RPE bumps was observed in 94% of eyes and pigment epithelium detachment (PED) in 11.8% of eyes, compared to 8% of eyes with RPE bumps and no PED observed in normal control eyes[23].

Special attention has been addressed to the layer of inner segment/outer segment (IS/OS) junction in different retinal disorders. The level of disruption to this layer in different retinal disorders has an excellent correlation with visual acuity[24-27]. That correlation is also maintained in patients with CSCR[18,28-30]. The length of IS/OS dis-

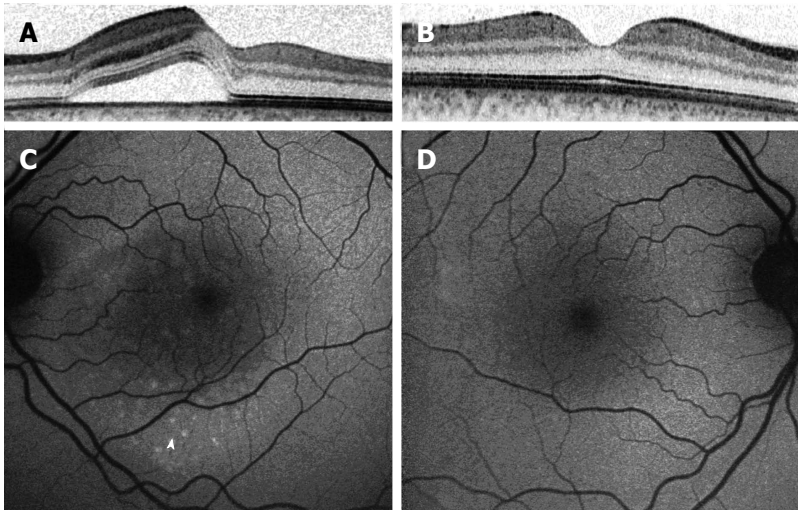

Figure 4 Imaging of a 38-year-old patient with central serous chorioretinopathy, one month following the beginning of his symptoms. Comparison of left (A) and right (B) eyes imaged with spectral domain optical coherence tomography shows a serous retinal detachment in his left eye. Minimal changes are seen with fundus autofluorescence imaging (C), consisting of a granular pattern of increased autofluorescence in the area of retinal detachment (arrowhead), compared to images of the right eye (D).

ruption, loss of foveal IS/OS and the level of integrity of the external limiting membrane layer were also found to be significantly correlated with visual acuity[31].

A newer generation of SD-OCT, swept-source OCT (SS-OCT), has also been investigated in patients with CSCR[32,33]. Ferrara *et al*[32] investigated the images of 15 eyes with chronic CSCR using SS-OCT. They documented PEDs in all eyes, as well as morphologic changes in the choroid underneath observed RPE changes and beyond these changes. They also observed focal and diffuse vascular dilation at the level of the choriocapillaris in half of the enrolled eyes, and at the level of Sattler's and Haller's layers in all eyes[32].

Fundus autoflouresence

Fundus autoflouresence (FAF) images were also shown to have an added value in the understanding of CSCR pathophysiology. Images of patients through different stages of the disease show a variety of autoflouresence phenomena, implying an ongoing damage to the RPE and photoreceptors. While Patients imaged within the first month following diagnosis have minimal abnormalities seen in their FAF photography (Figure 4), the next months are characterized by an increased hyperautofluorescent in the detached area of retina[34-36]. Some hyperautoflouresence appears as a granulated process, in correspondence to pinpoint subretinal precipitates[37]. The material often gravitates inferiorly or is shown to be collected in deposits at the border of the detachment[34]. These patterns are demonstrated in Figure 5. After resolution of subretinal fluid, the hyperautofluorescence of the fundus abates, suggesting that the accumulated material could be cleared with time. The chronic phase of the disease is characterized by varying degrees of atrophy, including areas of geographic atrophy and areas within fluid tracts descending inferiorly[34] (Figure 6). Areas of chronic leaks can have decreased autofluorescence surrounding them. These areas of hypoautofluorescence appear to expand in size with increasing chronicity of the disease[38]. In chronic CSCR eyes, inactive disease can be differentiated from an active disease by the lack of hyperautoflouresence, with only the atrophic component remaining as areas of hypo-autofluorescence[34] (Figure 7).

Multifocal electroretinography

The main advantage of multifocal electroretinography (mfERG) is the ability to demonstrate a persistent depression despite the resolution of the accumulating subretinal fluids. Hence, it has been investigated as a follow up tool for patients with chronic or recurrent CSCR as well as for examination of the seemingly healthy fellow eye[39]. It has been argued whether the pathologic findings in mfERG correspond with and are limited to the clinically observed areas of detachments or extend beyond these areas[39-41]. Excellent correlation was observed between changes in mfERG and function[42]. In a cross-sectional observational study by Lai and colleagues on 45 eyes with acute CSCR, it has been demonstrated that despite the fact that the outer retinal dysfunction is mostly localized to the central macula, a more widespread impairment in the more peripheral macula exists in the inner layers of the retina[43].

Macular microperimetry

Visual function evaluated only by the measurement of visual acuity may underestimate the level of impairment in patients with macular diseases[44-49]. Macular microperimetry was designed to detect more subtle defects in visual function in these patients by measuring retinal sensitivity within the central visual field[50,51]. The device can also serve as a follow up tool due to its image-registration facility. Reduced retinal sensitivity is observed in areas with previous subretinal fluids[28]. This reduced sensitivity also corresponds with RPE irregularities found on OCT[52].

NEW INSIGHTS ON TREATMENT MODALITIES FOR PATIENTS WITH CSCR

Acute CSCR is a self-limited disease in the majority of cases, with good final visual outcomes. The common management of acute CSCR still remains observation

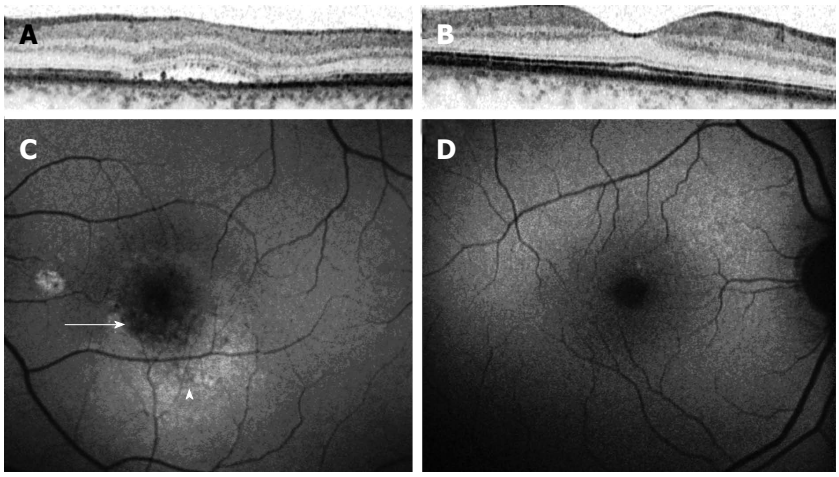

Figure 5 A 36-year-old patient with central serous chorioretinopathy, six months following the beginning of his symptoms. Comparison of left (A) and right (B) eyes imaged with spectral domain optical coherence tomography shows a serous retinal detachment in his left eye. In fundus autofluorescence imaging of the left eye (C) note the hyperautofluorescent in the detached area (arrow) beginning to form the manner of inferior gravitation (arrowhead), compared to images of the right eye (D).

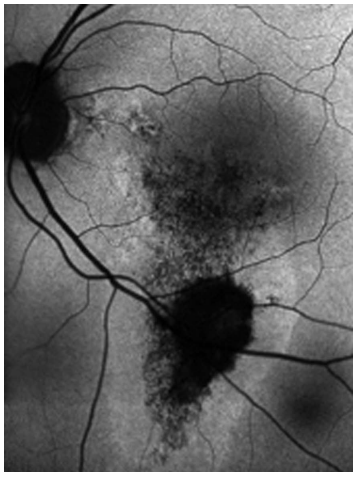

Figure 6 Fundus autofluorescence of a patient with chronic central serous chorioretinopathy showing inferior gravitational tracks and areas of decreased autofluorescence corresponding to areas of atrophy.

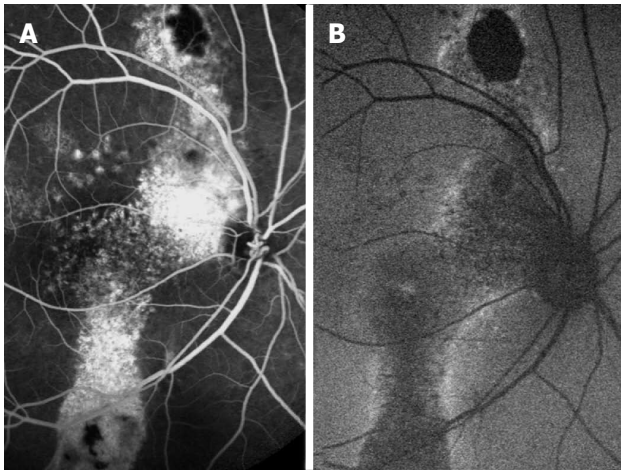

Figure 7 Chronic central serous chorioretinopathy; imaging from the same eye. Fluorescein angiography (A) with extensive hyperfluorescent areas, corresponding to areas of atrophy, seen as areas of decreased autofluorescence (B). Note the inferior gravitation pattern in both images.

and risk modification, with the exception of certain indications prompting immediate medical management. The common indications for the initiation of treatment are non-resolved subretinal fluid for 3 mo, decreased visual acuity from CSCR in the fellow eye or the need for immediate visual acuity rehabilitation. However, chronic CSCR as well as frequent recurrences of serous detachments may lead to RPE atrophy and other changes in the neurosensory retina leaving the patient with impairment of visual function[53]. Therefore, earlier treatment in selected patients may improve the final outcome and even prevent further damage.

Focal argon laser photocoagulation

Treatment with argon laser may be applied to small extrafoveal leaks on FA, mainly to shorten disease duration. Long term follow up results for argon laser treatment demonstrate no advantage over observation regarding final visual outcome, rate of progression to chronic CSCR or number of recurrences[54-56]. The main disadvantages of this treatment are the limited ability to affect final prognosis, the need for specific extrafoveal lesions to perform the procedure and possible side effects including the growth of new choroidal neovascularization (CNV)[56].

Photodynamic therapy with verteporfin

Standard dose photodynamic therapy (PDT) with injection of verteporfin has been shown to completely resolve serous detachment in 60%-80% of patients and to have a partial affect in the remaining patients[57-60]. However, serious side effects such as sudden visual loss, new CNV and atrophy of the RPE, had led to reduced-fluence treatment development[61,62].

Randomized and non-randomized trials on reduced-fluence PDT have found this treatment to be as effective as full-fluence therapy in regards to fluid resolution and functional outcome. Chan and colleagues performed a double masked randomized controlled trial on 63 eyes with acute CSCR treated with either half-dose PDT or placebo[63]. One year following treatment, approximately 95% of eyes in the PDT group compared to 58% in the placebo group had no subretinal fluid on OCT. Visual acuity at one year follow up was improved or stabilized in all patients in the PDT group compared to approximately 79% of patients in the placebo group[63]. Wu and

colleagues observed an improvement in mfERG in 24 eyes with acute CSCR, compared with 10 eyes in placebo group[64]. New imaging modalities, such as microperimetry, demonstrated the efficacy of PDT, beyond improvement in visual acuity[65-67].

There is still an ongoing search for the best way to reduce PDT dose, either by decreasing the laser therapy time, lowering the laser energy, altering the time interval between injections of verteporfin or lowering the dose of verteporfin. Zhao *et al*[68] conducted a research testing different doses of verteporfin for CSCR patients. Their conclusion was that 30% of the standard dose was optimal both for achieving fluid resolution and for avoiding adverse events[68].

In order to compare half-dose PDT to argon laser, Lim and colleagues prospectively assessed 26 eyes with CSCR[69]. Their results showed an earlier anatomic and functional resolution after treatment with half-dose PDT compared to laser. These differences, however, were no longer noted 3 mo following treatment[69].

Clinical response for this treatment has been linked to the level of hyperfluorescence observed on ICGA[70]. Patients with intense hyperfluorescence were more likely to show resolution of the serous detachment compared to patients with mild or no leaks observed on ICGA prior to treatment[70]. A recent report by Kim *et al*[71] evaluated the efficacy of half-dose PDT targeting the focal leakage point on FA for acute CSCR. In this retrospective trial, all 10 eyes treated in this manner had complete resolution of subretinal fluid compared to 27.3% of eyes receiving no treatment. These differences were minimized at 12 mo follow up; with 90% of PDT group and 63.6% of observation group showing no subretinal fluid. No differences were noted in final visual acuity or recurrence rates between the two groups[71]. Therefore, this treatment protocol may serve as a substitute for focal argon laser treatment for hastening absorption of subretinal fluid.

Other treatment modalities

Anti-vascular endothelial growth factor agents: Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents have dramatically changed the anatomical and functional prognosis of patients with retinal and choroidal diseases[72-74]. However, in patients with CSCR, improvement in prognosis following injections is more questionable, and anti-VEGF agents are not considered first line treatment. Despite the fact that VEGF levels were not found to be elevated in the aqueous humor of eyes with CSCR, many uncontrolled studies reported favorable results for anti-VEGF agents[75-84]. The largest series to date published by Lim *et al*[75] included 40 eyes in a prospective interventional case series. In their study, following one or two injections, 82.5% of patients achieved resolution of subretinal fluid at 4 mo follow up. However, they only included patients with acute CSCR, known to have a better prognosis; with no comparison arm for this study, and a relatively short follow up period[75].

A recent prospective, randomized study by Bae and colleagues compared ranibizumab injections to low-fluence PDT in 16 eyes with chronic CSCR[85]. Their conclusion was that the effect of ranibizumab was not promising compared with that of low-fluence PDT, in terms of anatomic outcomes. An important observation was that 50% of eyes in the ranibizumab group accomplished complete resolution only after they underwent additional low-fluence PDT[85].

A meta-analysis, conducted by Chung *et al*[86], identified four clinical controlled studies evaluating the effects of intravitreal bevacizumab injection in CSCR. In their data analysis, no significant differences in BCVA or central macular thickness (CMT) were found at 6 mo after injection between the bevacizumab group and the observation group. Another important issue they raised was that no report assessed severe complications or side effects of these intravitreal injections in patients with CSCR[86].

Micropulse diode laser

The main advantage of diode laser over argon laser is deeper penetration, reaching the choroid, mainly implicated as the pathologic origin of the subretinal fluid[87]. That sets the theoretical basis for the trials investigating the role of this laser in CSCR, as an attractive replacement for focal argon laser treatment. Verma and colleagues conducted a small randomized trial comparing the results of these two types of lasers in patients with acute CSCR[88]. Despite the fact that visual acuity was better in the diode laser treatment group 4 wk following the procedure, this difference was no longer observed 4 wk later[88]. Micropulse diode laser is considered less damaging to the RPE and photoreceptors, by applying short multiple pulses of energy instead of continuous energy. However, unlike the argon laser, the micropulse diode laser is less widely available and does not cause retinal bleaching guiding the operator when to stop laser application. In addition, micropulse diode laser was not proven to be safer or more effective than argon laser or PDT, and still requires a focal leak as seen on FA to guide treatment[89]. Therefore, the role of this laser as a substitute for conventional laser is still questionable.

Corticosteroid antagonists

The basis for corticosteroid antagonists administration for CSCR is the association found between the development of the disease and endogenous hypercortisolism (Cushing's syndrome)[90]. The hypothesis is that if this association exists with other hypercortisolemic states, than blocking the effect of corticosteroids may play a role in treating CSCR[91]. That hypothesis is further supported by the elevated serum cortisol levels commonly found in patients with CSCR[92-94]. The proposed medications, including ketoconazole, mifepristone (RU486), finasteride, rifampin, and anti-adrenergics, have not been tested in randomized, controlled trials.

Ketoconazole, an adrenocorticoid agent, has been investigated by two groups for the treatment of CSCR. In a prospective, case control study, Golshahi and colleagues

treated 15 patients with new onset subretinal fluid with 200 mg of ketoconazole per day for 4 wk[95]. No statistically significant benefit was found for that dosage[95]. An increased dose of 600 mg per day for 4 wk was later adminstered by Meyerle *et al*[96]. The results of this prospective, uncontrolled pilot study on 5 patients with chronic CSCR showed reduced serum cortisol levels, stable visual acuity, and anatomic improvement at 8 wk. They suggested larger, controlled trials to test the efficiency of ketoconazole in CSC patients[96].

Nielsen and colleagues treated 16 chronic CSCR patients with mifepristone (RU486), an active anti-glucocorticosteroid and anti-progesterone agent[97]. Favorable response was seen, with seven subjects gaining five or more letters of vision and seven subjects with improved OCT findings. Despite the fact that treatment was well tolerated without serious adverse effects in these patients, main obstetric concerns regarding this drug still limit its use[97].

Anti-adrenic agents, proposed to cause reduction of the adrenergic drive induced by stress, were also investigated for the treatment of CSCR. In his monkey model for experimental CSCR, Yoshioka suggested that inhibition of adrenergic receptors, particularly alpha receptors, may be beneficial[98]. Later studies investigating beta-blocking agents have shown partial improvement in CSCR patients, with no difference found between selective and non-selective agents[99-102]. However, none of the studies were controlled or randomized, and significant systemic side effects further limit the use of these agents.

Aspirin

The hypothesis that hypercoagulability plays a role in the pathogenesis of CSCR was based on a previous work showing increased levels of plasminogen activator inhibitor in patients with CSCR, compared to controls[103,104]. Caccavale and colleagues treated 107 CSCR patients with 100 mg acetyl salicylic acid (aspirin) once daily for one month and then every other day for five months[105]. A rapid recovery of visual acuity was observed after the first week of therapy, with low recurrence rate[105].

Anti-bacterial and anti-viral therapy

The hypothesis that an inflammatory damaging process has a role in the pathogenesis of CSCR is based on the characteristic of the disease. The proceeding stress as well the recurrent episodes of the disease have led investigators to consider a viral or a bacterial etiology.

The most investigated infectious association to CSCR is between the disease and *Helicobacter pylori* (*H. pylori*) infection[106-110]. Some investigators have noted a beneficial effect for *H. pylori* treatment in patients with CSCR[111,112]. In a randomized, controlled trial, twenty-five *H. pylori*- infected acute CSCR patients were treated with an anti-*H. pylori* treatment; another twenty-five patients with the same clinical presentations served as the control[112]. Subretinal fluid reabsorption time was significantly reduced in the treatment group, with no beneficial effect observed for final visual acuity[112]. Larger studies to confirm the association between H. pylori and CSCR are warranted.

Regarding a viral etiology, no large studies to establish the association between CSCR and any virus were published. Rathschuler *et al*[113] reported two cases of acute CSCR immediately started with an antiviral therapy (Acycloguanosine), with immediate regression of symptoms accompanied by an anatomic resolution of the leakage and the detachment. Larger studies to confirm the association between *H. pylori* or a viral etiology and CSCR are warranted.

CONCLUSION

CSCR is a common cause of visual impairment, especially in the middle aged population. Despite the fact that most patients will have spontaneous recovery, those with recurrent episodes or chronic disease may remain with significant functional impairment. The exact pathophysiology leading to subretinal fluid accumulation remains undetermined, but it is probably a combination of choroidal and RPE pathology. While imaging is evolving rapidly, the clinical implications of all these new imaging modalities are less clear. Treatment is still a subject of dispute, regarding indications, proper initiation time and type of treatment for both acute and choronic CSCR. That is mainly due to the fact that large randomized trials are still lacking.

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