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Review Article

Subthreshold Micropulse Laser Photocoagulation in the Management of Central Serous Chorioretinopathy

Nisreen S. Ezuddin, BS[1], Nicole L. Lanza, MEd[1], Christina Y. Weng, MD, MBA[2*]

[1]*University of Miami Miller School of Medicine, Miami, Florida*

[2]*Baylor College of Medicine-Cullen Eye Institute, Houston, Texas*

**Corresponding author: Dr. Christina Y. Weng, M.D., M.B.A., Baylor College of Medicine-Cullen Eye Institute, 1977 Butler Blvd., Suite E3.100, Houston, TX , USA, 77030. Tel: +1 713 798 6100; Email: Christina.Weng@bcm.edu*

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Abstract

Central serous chorioretinopathy (CSCR) is a condition characterized by serous retinal detachment with one or more leakage points in the choriocapillaris. The pathophysiology of CSCR is not completely understood, but its manifestations can be visually debilitating. While many cases of CSCR spontaneously resolve, some patients experience persistent or recurrent disease. Subthreshold diode micropulse (SDM) laser treatment has a potential role in the treatment of CSCR. This review will focus on the use of micropulse laser as a treatment modality for patients with this condition.

Keywords: central serous chorioretinopathy, subthreshold diode micropulse laser, CSCR management, central serous retinopathy, CSR, CSCR

Introduction

Central serous chorioretinopathy (CSCR) is a condition characterized by a serous neurosensory detachment, with or without retinal pigment epithelial (RPE) detachment, and is typically associated with one or more leakage points in the choriocapillaris that lead to fluid accumulation in the subretinal space [1, 2]. It is primarily seen in young healthy males in the fourth or fifth decades of life, but can also affect elderly patients. Although there is no clear racial predilection, it occurs more frequently in Caucasians, Asians and Hispanics. CSCR classically presents unilaterally and is characterized by blurred vision; other symptoms include metamorphopsia, relative central scotoma, micropsia, mild dyschromatopsia, and reduced contrast sensitivity [2, 3].

A diagnosis of CSCR is made utilizing a combination of clinical history, ophthalmoscopic examination, enhanced-depth imaging optical coherence tomography (EDI-OCT), fluorescein angiography (FA), and indocyanine green angiography (ICG) [1]. Biomicroscopic examination typically reveals the presence of serous detachment of the neurosensory retina in the posterior pole. EDI-OCT may assist in confirming the location and quantity of subretinal fluid as well as choroidal thickening. FA often shows a pinpoint leak at the level of the RPE, although multiple leaks can be observed, especially in atypical or recurrent cases [2].

While the choroid, RPE, and hormonal factors presumptively all play a role in the pathogenesis of CSCR, its etiology remains unknown. One recent publication postulates that CSCR results from choroidal vascular hyperpermeability related to stasis, ischemia, inflammation, or a combination of all three factors [2, 4]. Corticosteroids also alter the regulation of epithelial water and ion transport, which may impair the barrier function of the RPE [2, 5].

Central serous chorioretinopathy can be classified into acute or chronic forms. Acute CSCR often manifests as a single neurosensory retinal detachment lasting less than six months. Patients generally have a good prognosis with minimal visual sequelae [4]. Chronic CSCR is often characterized by multiple foci of neurosensory detachments and leakage points on FA [1]. Chronic CSCR patients have a poorer visual prognosis and often have persistent or recurrent disease leading to RPE atrophy, which contributes to inefficient resorption of subretinal fluid [2, 4]. One third to one half of all CSCR patients will experience a recurrence of the condition in their lifetime, and up to 5% of patients will suffer from severe vision impairment [6].

As 90% of CSCR cases resolve spontaneously within 2 to 3 months, treatment is usually initiated only after three months without resolution [7]. Given the association between corticosteroids and CSCR, physicians should counsel all patients to eliminate or reduce stress and corticosteroid-containing medications [6, 8]. For patients with persistent disease, a variety of treatments has been studied; these are discussed below, followed by a review of an emerging treatment modality, subthreshold diode micropulse (SDM) therapy.

Conventional Treatments

Focal laser photocoagulation

Focal laser photocoagulation occludes vessels at the site of exudation and allows RPE cells to pump fluid back into the choriocapillaris [7]. In a prospective, randomized trial of 67 patients with CSCR, average time to recovery-defined by retinal flattening and absence of leakage on FA-was only 6 weeks compared to a 16-week recovery time in the control group [9]. Laser photocoagulation can lead to scotomas and choroidal neovascularization (CNV) formation [10]; precise targeting of the laser beam can also prove challenging. The NAVILAS focal photocoagulation system (NAVILAS; OD-OS GmbH, Teltow, Germany) aims to minimize the latter by utilizing a retinal by utilizing a retinal eye-tracking laser delivery system with integrated digital color fundus photographs, red-free and infrared imaging, and fluorescein angiography that can be visualized in real-time. It was found to be effective in treating diabetic macular edema in a small series where patients experienced improved visual acuity and decreased central foveal thickness [11]. Chhablani, et al. evaluated the use of the NAVILAS system in CSCR patients in a prospective study found that FA-guided treatment to leakage points resulted in complete resolution of subretinal fluid in 15 out of 16 eyes in the study, although a change in visual acuity was not observed [12].

Indocyanine green angiography-guided photodynamic therapy

Indocyanine green angiography (ICG)-guided photodynamic therapy (PDT) induces temporary hypoperfusion of choroidal vessels [8]. In a prospective case series of 26 refractory CSCR patients, patients treated with PDT were observed to have a more rapid resolution of CSCR compared to their counterparts treated with laser photocoagulation, but no visual acuity difference was seen between the two groups [13]. Some believe that complications of PDT—which include RPE atrophy, choroidal ischemia, and CNV—may be minimized by using half-fluence PDT and half-dose verteporfin [6, 14].

Anti-vascular endothelial growth factors

Although elevation of VEGF levels has not been found in CSCR patients compared to controls, the utility of intravitreal anti-VEGF agents has been evaluated [15]. A prospective, controlled study of 30 patients with chronic CSCR found that all 15 of the 15 patients treated with bevacizumab had stable or improved vision at 6 months as compared to only 10 of the 15 untreated patients [16]. In contrast, a randomized controlled trial of 12 patients by Lim, et al. found no significant differences in visual acuity, central retinal thickness, or remission duration between treated and control groups [15].

Mineralocorticoid inhibitors

The potential role of mineralocorticoid receptor activation in CSCR pathophysiology has long been explored [17]. A non-randomized case series of 13 chronic CSCR patients given oral eplerenone, a mineralocorticoid receptor antagonist, demonstrated a significant decrease in subretinal fluid and improvement of visual acuity [18].

Rifampin

Cytochrome p450 inducer rifampin is thought to accelerate the metabolism of endogenous steroids in the liver. Steinle, et al. reported a case study where one patient with chronic CSCR was treated with oral rifampin. After one month, all subretinal fluid resolved, and the patient had improved visual acuity [19].

Ketoconazole

Ketoconazole inhibits endogenous cortisol synthesis by blocking both the conversion of cholesterol to pregnenolone and 11β-deoxycortisol to cortisol. In a controlled study of 30 patients with chronic CSCR, the treatment arm had improved visual acuity and decreased RPE detachment at 1 month compared with controls, but the difference was not statistically significant [20].

Mifepristone

Glucocorticoid receptor inhibitor mifepristone given orally to chronic CSCR patients for 12 weeks produced improvements in visual acuity in 7 patients in a case series conducted by Nielson, et al. Although all patients demonstrated a reduction in macular edema on OCT, mifepristone treatment did not resolve

subretinal exudates in all patients [21].

Acetazolamide

Carbonic anhydrase inhibitors appear to enhance retinal adhesiveness and subretinal fluid absorption in animal models [22]. In a prospective, non-randomized comparative trial of 22 patients, acetazolamide reduced subretinal fluid and accelerated resolution onset, but had no effect on CSCR recurrence or final visual acuity [23].

Adrenergic receptor inhibitors

Inhibition of adrenergic receptors has been evaluated in the treatment of chronic CSCR. In two case studies by Tatham, et al., both patients treated with propranolol experienced resolution of symptoms and macular edema. One patient had a recurrent episode of CSCR, which resolved when retreated with propranolol [24].

Subthreshold Diode Micropulse Laser

Subtheshold diode micropulse laser treatment consists of short, repetitive pulses of diode laser (0.1-0.3 microseconds), which releases low energy per pulse as opposed to argon or diode lasers (e.g. 100-200 ms) which apply continuous energy [25]. These micropulses deliver a sublethal cellular thermal effect that does not spread laterally to other neuroretinal cells [25-27]. SDM does not cause retinal blanching nor does it leave a visible scar [25, 26]. SDM has been used for the treatment of macular edema, branch retinal vein occlusion, glaucoma, and diabetic retinopathy [27-30]. Its long-term safety profile, with no ophthalmoscopically detectable laser lesions based on ANSI Z136.1 laser safety standards, was supported by Luttrull, et al. who applied SDM (800-950 mW, 0.1-0.3 ms pulse duration) in a confluent pattern over areas of retinal thickening in patients with diabetic macular edema [30, 31].

The use of SDM in the treatment of CSCR was pioneered by Bandello, et al. in 2003 [32]. Five eyes with CSCR were treated with SDM laser and demonstrated complete resorption within one month with no recurrence at the 4 month follow-up visit. Subsequent studies support that SDM laser provides therapeutic benefits similar to those of continuous wave laser without causing CNVM lesions or laser-related scotomas [26, 32-34].

In a prospective, randomized, double-blind sham controlled pilot study, five patients were placed in the sham group, and 10 patients were treated with subthreshold 810-nm diode micropulse laser. At the three month follow-up, mean BCVA improved from 35.4 letters ± 11.6 at baseline to 47.9 letters ± 8.0 at three months (P=0.06) in the treatment group with no significant improvement in the sham group [1].

Behnia, et al. conducted a randomized, controlled interventional trial of 37 acute CSCR patients experiencing symptoms for less than one month [35]. 18 patients were assigned to the control group and 19 to the experimental group, and follow-up visits were scheduled at 1 and 6 months post-treatment with micropulse laser. At each follow-up visit, contrast sensitivity was tested using CSV1000 grating charts in spatial frequencies of 3, 6, 12, and 18 cycles per degree (CPD). Six-month post-treatment contrast sensitivity in the experimental group was significantly improved as compared to the controls for spatial frequencies of 6 and 12 CPD. The treatment arm scored 5.54 ± 0.66, and the control arm scored 4.7 ± 0.95 (p=0.021) at 6 CPD. At 12 CPD, the treatment arm scored 4.77 ± 0.73 while the control arm scored 3.9 ± 0.88 (p=0.017).

In a retrospective, interventional case series, 11 eyes with CSCR were treated with low-intensity/high-density subthreshold 810-nm micropulse diode laser to areas of leakage seen on FA and to areas of neurosensory detachment and/or pigment epithelial detachments. There was a significant decrease in the macular thickness (mean=97 μm, p=0.0046) and an overall improvement in visual acuity from 39.2 letters pre-treatment to 45.4 letters post-treatment (p-value not reported) with no evidence of post-treatment RPE damage [31]. This study provides evidence that low-intensity/high-density SDM laser treatment is safe and effective for CSCR treatment.

Chen, et al. treated 26 eyes with chronic CSCR and juxtafoveal leakage on FA in a prospective, non-comparative interventional case series [26]. The eyes were divided into 3 groups—focal leakage with no associated RPE atrophy (group 1), focal leakage with RPE atrophy (group 2) and diffuse RPE decompensation with indeterminate source leakage (group 3). Group 1 patients had complete resolution after 1 SDM treatment. In group 2, eight eyes had total subretinal retinal fluid (SRF) reabsorption after 1 to 3 SDM sessions, while 1 patient had persistent SRF. In group 3, however, 5 of 11 eyes with diffuse juxtafoveal leakage required supplemental PDT laser therapy to achieve full resolution of SRF. The average preoperative foveal thickness at the six month follow-up was reduced by more than half of its original thickness. 15 eyes (57.7%) gained three or more lines of vision while 6 eyes (23.1%) gained one to three lines. The authors conclude that while SMD laser is beneficial for patients with point source leakage, it has limited use for those with RPE atrophy or diffuse RPE decompensation who likely require PDT for SRF resolution.

In a prospective case series of 24 eyes of 22 patients with CSCR duration greater than three months, patients were treated with 810 nm micropulse diode laser [32]. 14 eyes required only one treatment, nine eyes received two to three treatments, and one eye had 5 treatments within three years. At the one-month follow up, nine eyes achieved complete resorption of SRF, and the mean retinal thickness decreased from 327 μm pre-treatment to 197 μm post-treatment. By the end of the three-year follow

up period, two-thirds of the treated eyes achieved complete resorption of SRF; the median visual acuity of treated eyes improved from 20/32 to 20/25 (p=0.062), and mean retinal thickness decreased from 328 μm to 168 μm (p<0.0001). Only two eyes demonstrated worse visual acuity, by one and five lines, at the end of the study.

In an interventional prospective non-comparative case series of seven patients with CSCR with active leakage sites and serous detachment persisting for over six months, Ricci, et al. studied the use of SDM laser treatment 15 minutes after injecting 25 mg of ICG in 2 cc of 5% glucose solution. All patients demonstrated an increase in visual acuity and reduction of subretinal fluid by 7-14 days post-treatment. Within 4 to 8 weeks, five patients had complete resolution of SRF, and two patients had reduced SRF. Of the five with complete resolution, none had a recurrence at the 12 month follow-up, while the other two patients experienced no worsening of the SRF or visual acuity. Ricci, et al. concluded that ICG-enhanced SDM laser treatment is safe and effective in CSCR patients with serous retinal detachment, and may assist in verification of SDM laser placement [34].

Discussion

CSCR is often self-limited, but for persistent or recurrent disease, treatment should be considered. Although there have been many studies evaluating various pharmacological agents in the treatment of CSCR, most lack statistical power due to small sample sizes, lack of controls to diminish the effect of confounding variables, and failure to randomize patients.

Variable success has been observed with mineralocorticoid inhibitors, rifampin, ketoconazole, mifepristone, acetazolamide, vascular endothelial growth factor inhibitors, and adrenergic receptor inhibitors; no definitive evidence exists that they are superior to observation alone.

The principal advantage of SDM over other laser treatment modalities is a decreased risk for scotoma or CNVM formation. SDM may also be beneficial in the treatment of refractory cases of CSCR, as suggested by Lanzetta, et al [32]. One study demonstrated that SMD-treated CSCR patients had improved contrast sensitivity over untreated controls [35]. Large-scale, randomized controlled trials are needed in order to determine the true therapeutic benefit of SDM compared to observation or other treatment modalities. Perhaps the greatest limitation of SMD therapy is the difficulty in titrating the treatment dose given the absence of an ophthalmoscopically visible mark. This makes it extremely challenging for the surgeon to guide laser application, although staining RPE cells with ICG dye has been suggested as a potential solution [34, 36].

While data supporting the potential benefits of SDM laser therapy in CSCR is growing, the use of this treatment modality remains limited. This may be due to the fact that SDM laser machines are not widely available. Additionally, SDM laser has not yet proven to be more efficacious than focal laser for extrafoveal lesions, and there is no evidence that it is safer than PDT when there is a juxtafoveal RPE leak. It shares a similar drawback with focal argon laser in that its efficacy diminishes when there is diffuse RPE leakage [25, 26]. Due to incomplete understanding of SDM's exact mechanism of action, no well-defined treatment protocol exists in regards to the optimal laser irradiance (power per unit of area) that should be delivered to the retina [36].

Conclusion

In summary, subthreshold diode micropulse therapy may be a useful treatment modality for idiopathic chronic CSCR. Its inherent property of utilizing less energy and thereby minimizing chorioretinal disruption is appealing. However, randomized controlled trials are needed to establish long-term efficacy, identify which patients may benefit most from SDM treatment, and determine whether SDM is in fact superior to alternative treatment approaches. Given the limited but promising data thus far, further investigation is merited.

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