

Efficacy of the subthreshold micropulse yellow wavelength laser photostimulation in the treatment of chronic central serous chorioretinopathy

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Abstract

• **AIM:** To evaluate the efficacy and safety of subthreshold micropulse yellow laser (SMYL) in the treatment of chronic central serous chorioretinopathy (CCSC).

• **METHODS:** The medical records of 58 eyes of 58 patients with CCSC were reviewed. A 577-nm SMYL system was used for the treatment. Fundus fluorescein angiography was used as the primary method of identifying CCSC, and resolution of subretinal fluid (SRF) evaluated by optical coherence tomography (OCT) and fundus autofluorescence. Central macular thickness (CMT), central macular volume (CMV), total macular volume (TMV), subfoveal choroidal thickness (SFCT), subretinal fluid height (SRFH), and subfoveal fluid basement diameter values were measured by spectral domain-OCT (SD-OCT) for all eyes.

• **RESULTS:** The mean age of the patients was 42.4±9.9 (range: 20-72)y. The mean follow-up was 11.4±8.5 (range: 6-37)mo. Median BCVA at the final follow up after treatment was statistically significant from the baseline. Complete SRF resolution was 12.1% of the eyes in the 1st month, 67.2% of the eyes in the 3rd month and 67.2% of the eyes in the last follow up. The initial median CMT, CMV, TMV, and SFCT values before treatment was significantly higher than 3rd month visit values ($P<0.001$). In the multivariate analysis performed, age and disease duration were found to be a risk factor for persistent SRF ($P=0.017$, $P=0.016$, respectively).

• **CONCLUSION:** SMYL treatment provides a significant anatomical and functional improvement and is effective in eliminating SRF in eyes with CCSC.

• **KEYWORDS:** central serous chorioretinopathy; subthreshold micropulse laser; optical coherence tomography

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INTRODUCTION

Central serous chorioretinopathy (CSC) is a chorioretinal disease with multifactorial etiology that not fully elucidate the pathogenesis. Typically, it is characterized by serous detachment of the neurosensory retina in the posterior pole, and mostly affecting young to middle-aged men^[1]. The disease is sporadic and although it may affect both eyes symmetrically, it is usually unilateral^[2]. Though spontaneous resolution is seen in the majority of patients, it may cause significant visual morbidity in chronic disease. This chronic condition has been shown to have more common retinal pigment epithelium (RPE) abnormalities and is a different subtype named diffuse pigment epitheliopathy^[3]. The majority of acute CSC spontaneously resolves within 3mo of the onset of symptoms^[4]. The disease duration required for CSC to be called chronic disease varies from author to author; some authors state 3mo^[5] and some authors suggest that 6mo^[6] of unresolved subretinal fluid (SRF).

Risk factor changes (discontinuation of steroids), oral medications (anti-corticosteroids, adrenergic blockers, carbonic anhydrase inhibitors), intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors, diverse forms of retinal laser photocoagulation and photodynamic therapy can be mentioned in the treatment of chronic CSC (CCSC)^[4,7]. In order to reduce the damage that the photocoagulation may cause on the retina, the laser technique which aims to reduce the heat occurring in the retina and thus collateral damage by modifying the laser parameters such as power, duration and repetition of the laser is called “subthreshold”. Nowadays, subthreshold micropulse laser (SML) therapy is another treatment option that has been increasingly used in the treatment of CCSC^[4].

SML is thought to act by increasing the temperature up to the therapeutic level and below the level of tissue damage in the chorio-retino-rpe complex, thus minimizing the induced photothermal damage and no visible burns, necrosis, scotoma or collateral damage occurs^[8-10]. Micropulse laser treatment offers a number of potential advantages over conventional photocoagulation, such as providing treatment option in foveal region, increased color vision and contrast sensitivity without tissue damage, and provides the ability to retreat inadequate responses or recurrences^[11].

SML can be applied with either 810-nm or 577-nm wavelength lasers. The 577-nm yellow laser light is absorbed to the maximum level by both oxyhemoglobin and melanin^[12]. The efficacy of SML performed with 810-nm diode laser in CSC patients has been demonstrated in several studies previously^[13-17]. However, the average laser power was reported to be greater than the laser with a wavelength of 577-nm^[18]. This can be explained by the absorption of yellow wavelength laser beams by both oxyhemoglobin and melanin. The goal of this study to evaluate the efficacy and safety of subthreshold micropulse yellow laser (SMYL) in the treatment of CCSC.

SUBJECTS AND METHODS

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the patient included in the study.

Subjects A total of 58 eyes of 58 patients (47 males, 11 females) who were diagnosed with CCSC and treated with SMYL at the Harran University Faculty of Medicine, Department of Ophthalmology, from February 2016 through May 2019 were enrolled.

The inclusion criteria were as follows: symptomatic CSC of 3mo or longer, CCSC with SRF involving the fovea documented by spectral domain-optical coherence tomography (SD-OCT), patients who were eligible for monthly visit at least 6mo. Exclusion criteria were as follows: patients who had any systemic disease that may affect the eye (diabetes mellitus, Behçet's disease, *etc.*) or ocular disease or choroidal neovascularization (CNV) secondary to CCSC, patients who had received anti-VEGF treatment or conventional laser or photodynamic therapy (PDT) before SMYL treatment, patients who were not followed up over 6mo after the start of SMYL treatment.

Examinations All patients received comprehensive ophthalmic examination after enrollment. Best-corrected visual acuity (BCVA) was examined using a decimal visual acuity chart. Fundus fluorescein angiography (FFA), fundus autofluorescence (FAF), and SD-OCT (Spectralis

HRA; Heidelberg Engineering; Heidelberg, Germany) were performed at baseline. Patients with serous macular detachment of the neurosensory retina on SD-OCT (Spectralis OCT; Heidelberg Engineering, Germany) and with a single or multiple active leakage sites and if any RPE changes on fluorescein angiography (FA) were diagnosed as CSC. Central macular thickness (CMT), central macular volume (CMV), and total macular volume (TMV) values were measured by SD-OCT for all eyes. Subfoveal choroidal thickness (SFCT), subretinal fluid height (SRFH), and subfoveal fluid basement diameter was measured manually by a single ophthalmologist (Işık MU). A single technician performed the OCT measurements. Işık MU evaluated all choroidal thickness data using advanced depth imaging scans as the axial distance from the RPE to the outer choroid-sclera interface.

Treatment Procedure In this study, a 577-nm SMYL system (Supra 577Y Subliminal Laser System; Quantel Medical, Clermont-Ferrand, France) was used for the treatment. Laser application was performed with a Mainster contact lens (Ocular Instruments, Bellevue, WA, USA). Subthreshold treatment was performed in the micropulse mode, using a 160- μ m spot diameter and a 200ms duration with 5% duty cycle (0.1ms ON and 1.9ms OFF) energy. The power titration was started at 400 mW power with monospot micropulse model and a just visible minimal graying reaction on the retina served as the threshold burn. Fluorescein angiography-guided approach was preferred and in addition, an appropriate screening mode was selected to completely cover the edema area on the OCT thickness map. Micropulse laser was applied at central 1000 micron of the macula, and to the leaking areas if present outside the central 1000 micron of the macula, without space by reducing 50% of the power of visible burn. If the SRF was not completely resolved 3mo after the treatment or there was a recurrence after complete resolution, SMYL was repeated.

Follow up and Retreatment All patients were reviewed at 1, 3 and 6mo after the laser treatment. At follow-up visits, OCT, FAF, and BCVA were performed. If lack of complete resolution of SRF by 3mo and increase in SRFH after incomplete resolution, or "recurrence," that is, reaccumulation of SRF after previous complete resolution was observed in OCT, eyes were retreated.

Patients were divided into 3 groups. Group 1: eyes with complete resolution of SRF at the 3rd month follow-up after SMYL treatment; group 2: eyes with refractory SRF at the 3rd month follow-up after initial SMYL treatment; group 3: SRF occurrence after complete resolution at the follow up period (recurrence).

Statistical Analysis Analysis of the data was performed in the SPSS for Windows 21 (Armonk, NY: IBM Corp., USA). The descriptive statistics were expressed as mean \pm standard

Table 1 Comparison of demographic data and pretreatment OCT characteristics among groups

Items	Group 1 (n=33)	Group 2 (n=19)	Group 3 (n=6)	mean±SD/median (IQR)	P
Age (y)	43.4±6.9	43.6±10.2	51.6±10.7		0.061
Gender (male/female)	26/7	16/3	5/1		0.667
Follow-up (mo)	10.7±8.0	9.2±6.4	22.1±10.4		0.003
BCVA (logMAR)	-0.29±0.23	-0.35±0.18	-0.38±0.15		0.204
CMT (µm)	447 (387-560)	466 (345-513)	414 (365-436)		0.384
Subfoveal fluid height (µm)	220 (151-343)	252 (140-287)	212 (134-247)		0.462
SRF basement diameter (µm)	2932 (1833-4004)	3503 (2418-3940)	2464 (1736-3575)		0.470
CMV (mm ³)	0.36 (0.29-0.43)	0.34 (0.25-0.40)	0.34 (0.29-0.39)		0.252
TMV (mm ³)	9.43 (9.17-10.69)	9.53 (9.0-9.83)	9.08 (9.01-9.54)		0.147
SFCT (µm)	393 (310-482)	332 (311-376)	362 (244-562)		0.424

OCT: Optical coherence tomography; IQR: Interquartile range; BCVA: Best corrected visual acuity; CMT: Central macular thickness; SRF: Subretinal fluid; CMV: Central macular volume; TMV: Total macular volume; SFCT: Subfoveal choroidal thickness.

deviation (SD) for variables with normal distribution, median [interquartile range (IQR)] for non-normal distributions, and number of cases and percentages for nominal variables. The test used to examine the presence of normal distribution was the Kolmogorov-Smirnov distribution test. The Pearson correlation test for normally distributed data and the Spearman correlation test for non-normally distributed data were used. The complete absorption rate of SRF were analyzed by the Pearson χ^2 test or the Fisher exact test between the groups. In each treatment group, SRFH and CMT were compared to the repeated measures of test before and after treatment (1st month, 3rd month, and last follow-up). When the repeated measure test is performed, the values obtained are expressed as estimated mean value [standard error (SE)]. Univariate and multivariate regression analysis were used to analyze the non-responsiveness markers.

RESULTS

The mean age of the patients was 42.4±9.9 (range: 20-72)y. The mean follow-up was 11.4±8.5 (range: 6-37)mo after the treatment. There was no previous treatment before SMYL treatment. The laser power used in our study ranged from 200 to 600 mW.

The mean time from onset of symptoms to treatment (disease duration) was 5.1±1.0mo in group 1, 4.5±1.0mo in group 2, and 4.5±1.1mo in group 3 ($P=0.125$). There were no significant differences among the groups in age, gender, initial BCVA, SRFH, subfoveal fluid basement diameter, CMT, CMV, TMV, and SFCT values (Table 1). Median BCVA at 3mo after treatment was 1.0 Snellen (0.0 logMAR, mean 0.84±0.22 Snellen) and it was statistically significant from the baseline and 1st month BCVA values (0.22 logMAR, 0.1 logMAR, respectively). The median BCVA at final follow-up was 1.00 Snellen (0.0 logMAR). Furthermore, there was no significant difference between 3rd month and last visit BCVA values ($P=0.563$). In all patients BCVA improvement was observed.

Complete SRF resolution was 12.1% of the eyes in the 1st month and 67.2% of the eyes in the 3rd month. Nineteen eyes (32.8%) without complete SRF resolution underwent second session of SMYL, and 4 of these patients had complete resolution of SRF. All eyes in group 2 showed a significant decrease in SRF on SD-OCT; the average decrease in fluid height was 45% in 3mo and 65% at the last control. In 6 (10.3%) eyes within group 1, recurrence was detected at the 6th month control and 2nd session SMYL was applied, and 2 of them had completely SRF resolution. At the last follow-up, 39 (67.2%) eyes had complete resolution of SRF. Median SRF decreased to 0 µm (mean: 45.1 µm) at 3mo after treatment and it was significantly lower from the baseline and 1st month SRF values (median: 216 µm, mean: 250.9 µm; median: 128.5 µm, mean: 127.5 µm, respectively). The median SRF at final follow-up was 0 µm (mean: 45.1 µm) and it was similar to 3rd month SRF values ($P=0.1$). We performed repeated measures analysis of SRFH. We observed a significant decrease in SRFH over time in all 3 groups (Figure 1, Table 2).

The initial median CMT before treatment was 438 µm (mean: 455 µm), in comparison to 309 µm (mean: 328 µm) after 1st month and 226 µm (mean: 244 µm) at the 3rd month visit, respectively ($P<0.001$). The final median CMT was 220 µm (mean: 243 µm) and there was no significant difference between CMT values at 3rd month ($P=0.679$). We also performed repeated measures analysis of CMT. We observed a significant decrease in CMT over time in all 3 groups (Figure 2, Table 3). The pretreatment median CMV and TMV decreased from 0.34 and 9.35 mm³ to 0.25 and 9.09 mm³ at 1st month, respectively, and to 0.21 and 8.7 mm³ at 3rd month, respectively ($P<0.001$). The median SFCT before the treatment was 393 µm (mean: 410) and there was a significant increment after 1st month (median: 380.5 µm, mean: 383 µm) and at the 3rd month (median: 353.5 µm, mean: 362 µm; $P<0.001$). At the final visit, the median SFCT (348 µm) was similar to 3rd month SFCT values ($P=0.591$).

Table 2 SRFH values of different groups before and after SMYL treatment and comparison of these values with repeated measures analysis

Groups	Pre-SMYL	Post-SMYL 1 st month	Post-SMYL 3 rd month	Last follow-up	P
Group 1	268.9 (30.9) ^{b,c,d}	100.9 (17.8) ^{a,c,d}	0.0 (6.7) ^{a,b}	0.0 (6.8) ^{a,b,y,z}	<0.001
Group 2	280.4 (42.9) ^{b,c,d}	163.1 (24.7) ^{a,d}	124.4 (9.3) ^{a,d,x,z}	81.8 (9.5) ^{a,b,c,x}	<0.001
Group 3	172.2 (77.3)	177.7 (44.6) ^{c,d}	0.0 (16.8) ^{b,d}	52.5 (17.2) ^{b,c,x}	<0.001
P	0.462	0.074	<0.001	<0.001	

SRFH: Subretinal fluid height; SMYL: Subthreshold yellow laser. ^aSignificant difference between pre-SMYL measurements; ^bSignificant difference between post-SMYL 1st month measurements; ^cSignificant difference between post-SMYL 3rd month measurements; ^dSignificant difference between last follow-up measurements; ^xSignificant difference between group 1 at the same follow-up time; ^ySignificant difference between group 2 at the same follow-up time; ^zSignificant difference between group 3 at the same follow-up time.

Table 3 CMT values of different groups before and after SMYL treatment and comparison of these values with repeated measures analysis

Groups	Pre-SMYL	Post-SMYL 1 st month	Post-SMYL 3 rd month	Last follow-up	P
Group 1	475.0 (28.1) ^{b,c,d}	295.6 (18.4) ^{a,c,d}	207.8 (11.8) ^{a,b,y}	208.6 (12.3) ^{a,b,y}	<0.001
Group 2	473.0 (39.0) ^{c,d}	369.8 (25.5) ^d	301.9 (16.4) ^{a,x}	287.6 (17.0) ^{a,b,x}	<0.001
Group 3	401.7 (70.3)	395.5 (46.0) ^{c,d}	223.5 (29.6) ^{b,d}	263.5 (30.8) ^{b,c,x}	0.044
P	0.621	0.027	<0.001	0.002	

CMT: Central macular thickness; SMYL: Subthreshold yellow laser. ^aSignificant difference between pre-SMYL measurements; ^bSignificant difference between post-SMYL 1st month measurements; ^cSignificant difference between post-SMYL 3rd month measurements; ^dSignificant difference between last follow-up measurements. ^xSignificant difference between group 1 at the same follow-up time; ^ySignificant difference between group 2 at the same follow-up time.

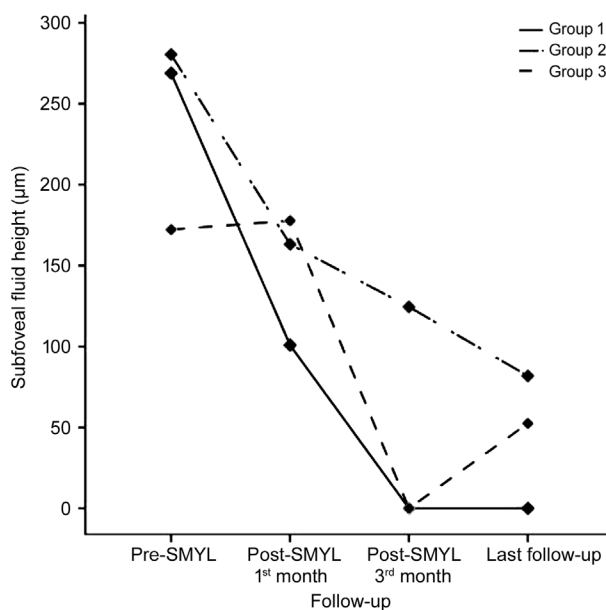


Figure 1 Linear graph of changes in subfoveal fluid height values of different groups before and after SMYL treatment.

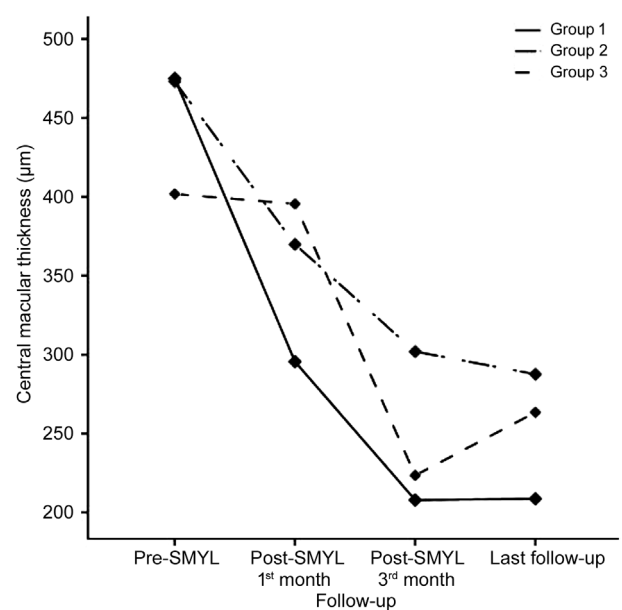


Figure 2 Linear graph of changes in CMT values of different groups before and after SMYL treatment.

We separated the group 1 as the responders, and the groups 2 and 3 as the non-responders, and then re-performed the statistical analysis. When multivariate analysis was performed by including age, gender, duration of the disease, and pre-treatment values such as, SRFH, subfoveal fluid basement diameter, CMT, CMV, TMV, and SFCT, the age and disease duration were found to be a risk factor for non-responsiveness ($P=0.017$, $P=0.016$, respectively). There was no retinal damage

or complications [such as laser-induced choroidal neovascular membrane (CNVM) or scars] were observed in association with the laser treatments in follow up period (Figure 3).

DISCUSSION

The presence of chronic SRF in CSC can cause photoreceptor death, which can lead to permanent vision loss and extensive RPE damage^[19-21]. The condition of RPE is very important in the pathophysiology and prognosis of the disease itself and

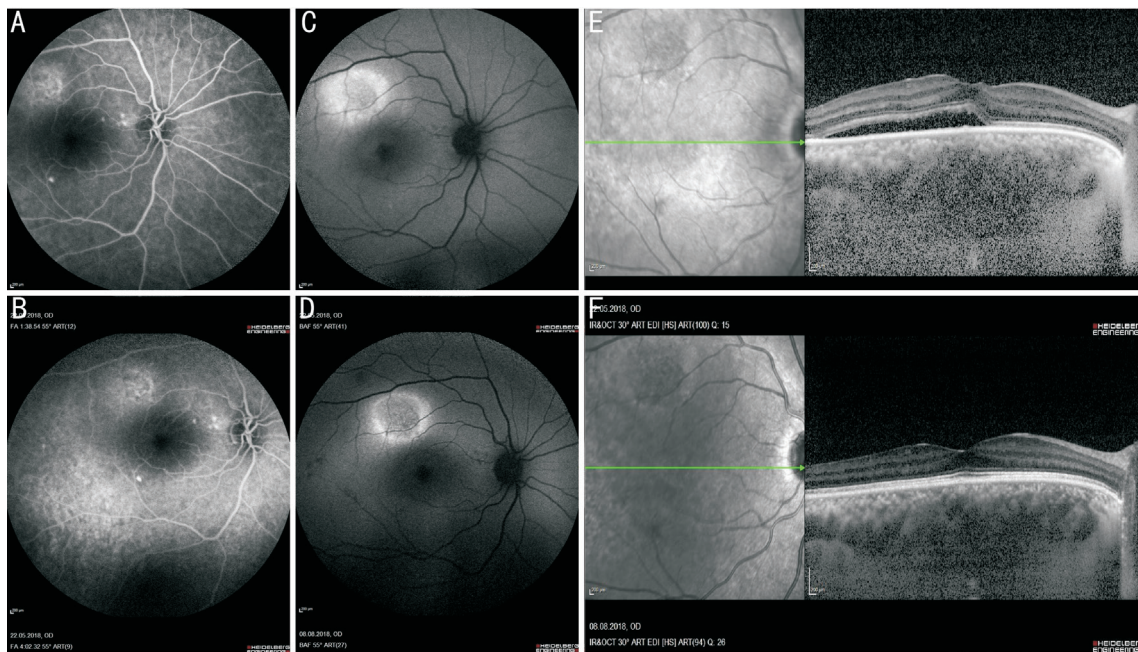


Figure 3 A 39 years old, male patient's images A: A frame from an early phase of fluorescein angiogram; B: A frame from a late phase of fluorescein angiogram; C: Fundus autofluorescence image before the treatment; D: Fundus autofluorescence image 3mo after the treatment; E: OCT image before the treatment; F: OCT image 3mo after the treatment.

Table 4 SMYL parameters used by the authors and complete SRF resolution rates at the third and final follow-up

Authors	Spot size (µm)	Exposure time (ms)	Duty cycle (%)	Subthreshold rate (%)	Complete SRF resolution rate at 3mo follow (%)	Complete SRF resolution rate at the last follow (%) (mo)
Zhou <i>et al</i> ^[25]	100	200	5	25	54.2	
Zhou <i>et al</i> ^[25]	100	200	5	50	83.3	
Roca <i>et al</i> ^[27]	100-200	200	5	50		92.4 (12)
Işık <i>et al</i> (current study)	160	200	5	50	67.2	67.2 (11)
Arsan <i>et al</i> ^[18]	160	200	5	50	82.0	92.3 (19)
Özmert <i>et al</i> ^[29]	160	200	5	50		80.0 (12)
Scholz <i>et al</i> ^[28]	160	200	5	50	30.0	24.0 (6)
Abd Elhamid ^[24]	200	200	10	50	74.0	87.0 (6)
Yadav <i>et al</i> ^[5]	100	200	10	50	40.0	

SMYL: Subthreshold micropulse yellow laser; SRF: Subretinal fluid.

should be considered for active treatment. Abnormalities of choroidal circulation, impaired autoregulation and dysfunction of the RPE barrier are believed to play an important role in the pathophysiology of the disease^[22]. The 577 nm SML is designed to minimize negative thermal effects on the neural retina and deeper structures, targeting RPE by establishing photostimulation^[7]. We evaluated the 577 nm wavelength laser providing a better titration by increasing the power until the visible burns occur in the peripheral retina. This may allow a more effective treatment while maintaining subthreshold treatment. However, the lack of a well-defined titration procedure and a wide variety of settings in various clinical trials have caused diversity in the results with this technology (Table 4).

There have been previous studies on the use of subthreshold retinal laser therapy for CCSC. Although visual acuity results

and improvement of CMT were achieved in short term, laser parameters and duration of follow-up in these studies show significant variability^[4]. Yadav *et al*^[5] assessed safety profile and treatment outcome of SMYL in CCSC patients. They reported significant decrease in fluid height in all eyes and complete resolution in six of 15 eyes (40%), although patients underwent only one session of treatment. When we look at the short-term results, SMYL seems to be more successful. In a study involving ten eyes of ten patients, subthreshold treatment was performed using 100 µm spot size and 20-ms duration with 15% duty cycle, the authors reported only one case with persistent SRF despite a total of four treatment sessions^[23]. Unlike our study they repeated SMYL until SRF was completely resolved in a monthly pattern. There were 4 patients who had previous anti-VEGF (3 patients) and conventional focal laser (1 patient). Also, half of the patients had follow-up

periods less than 6mo. Despite higher SRF resolution rate there were limitations of their study such as involving small number of patients, previously treated patients and very short-term follow-up periods of the patients. In another study, 3mo after the treatment, 73% of the eyes showed complete resolution which was close to our study^[24]. Zhou *et al*^[25] reported 70% complete SRF resolution at 1mo. When Zhou *et al*^[25] used the same parameters with 25% threshold power in the same study, complete resolution rate was reported as 30% at 1st month. In a study, using 70% threshold laser power, obtained 91% normal macular profile at 12mo^[26]. Roca *et al*^[27] have also reported higher complete SRF resolution rate (92.4%) at 12mo. Those different results may be related to the different mean age of patients, follow-up periods and laser parameters in these studies. Apart from these possible reasons, some of the authors applied the treatment to the leak area under the guidance of FA and some others applied the treatment to areas with thickness increase under the guidance of OCT. Also, this may be the reason for the difference in treatment success between different studies using the same parameters.

The study by Scholz *et al*^[28] involved 38 eyes of 38 patients with persistent SRF for at least 6wk, in 3rd month visit 30% of the eyes showed no SRF. They used the same laser parameters with our study and they reported 13% complete resolution at 1st month. Complete resolution rate after first treatment at 1st month was 12% in this study. The reason for the lower success of treatment in their study could be due to lack of follow-up of 15 patients. Özmert *et al*^[29] compared the efficacy of SMYL and low-fluence PDT in the treatment of CCSC. Fifteen eyes were treated with SMYL utilizing the same parameters as in our study. At the 12-month follow-up, 80% of the eyes achieved complete SRF resolution and they reported that none of the eyes were unresponsive to SMYL. In another study including 39 eyes of 39 patients with CCSC treated with SMYL, applying the same parameters as our's, the authors reported complete resolution of SRF in 82% of the eyes in 3mo^[18]. The duration of CCSC prior to treatment was 13.0±9.1mo in the study of Özmert *et al*^[29], and 14.67±2.86mo in the study of Arsan *et al*^[18]. In this study, the mean duration was 5mo. This period may have caused differences in success rates. As a matter of fact, the regression analysis revealed that short duration of disease was a risk factor for SRF resistance.

The current study demonstrates significant improvement in visual acuity. It also shows significant decrease in CMT, SRF height following SMYL treatment. In all previous studies, significant improvement in visual acuity were also reported^[5,8,18,23-25,27-29]. CMT and SRF height results are comparable to those of previous studies. They all reported significant decrease in CMT and SRF. We evaluated SFCT and observed significant decrease in all visits following

SMYL. In some previous studies, the authors also evaluated SFCT changes after SMYL. They reported improvement in SFCT^[8,18,27] except the study by Kim *et al*^[23] who reported no significant change in SFCT after SMYL.

Many patients needed repetition of SMYL in the current study and in the previous studies. Retreatment was done for eyes with persistent SRF (32.8%) or recurrent SRF (10.3%). In the study of Kim *et al*^[23], 50% of the patients received SMYL retreatment. In another study, authors reported the need for second treatment in 58% of the patients^[8]. Roca *et al*^[27] have reported relatively less retreatment ratio (17.5%). Despite this, several patients needed a repetition of the SMYL that further decreased the SRF. Nevertheless, even after retreatments, there was not any complication related to SMYL treatment in our study, such as laser induced CNVM or scar according to the FAF results. In previous studies which involved FAF imaging^[5,25-29], the authors also reported no retinal damage or complications related to the treatment.

Overall, we did not observe any adverse or unexpected effects during the follow-up period. Treatment very close to fovea can also be safely applied. This indicates that 577-nm SML therapy can be performed safely and repeatedly, but long-term follow-up studies are required to confirm long-term results. The main disadvantage of SMYL is the greater number of retreatments. Limitations of the current study include its retrospective design, the small sample size, the use of Snellen visual acuity, the lack of randomization and a relatively short follow-up.

In brief, our results demonstrated that SMYL is efficient and safe for treatment of the macula, and provides a significant anatomical and functional improvement and is effective in eliminating SRF in eyes with CCSC. As a noninvasive method, SMYL appears to be a safe method that can be repeated safely, is safer than conventional laser photocoagulation and PDT, is cheaper than intravitreal anti-VEGF treatments, provides fast, effective response and success in short time in visual rehabilitation. We recommend the use of SMYL in patients who do not have any additional pathology, as well as in patients resistant to other treatments, in patients with one eye, and in patients using corticosteroids mandatorily such as organ transplant, some rheumatoid disorders.

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