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Subthreshold Micropulse Laser (577 nm) Treatment in Chronic Central Serous Chorioretinopathy

Paula Scholz[a] Lebriz Ersoy[a] Camiel J.F. Boon[b] Sascha Fauser[a]

[a]Department of Ophthalmology, University Hospital of Cologne, Cologne, Germany; [b]Leiden University Medical Center, Leiden, The Netherlands

Key Words
Central serous chorioretinopathy · Subthreshold micropulse laser · Photodynamic therapy

Abstract
Purpose: To assess treatment with a 577-nm subthreshold micropulse laser (SML) in patients with chronic central serous chorioretinopathy (cCSC). ***Methods:*** This retrospective study included 38 patients treated with a 577-nm SML (Supra Scan; Quantel Medical) for cCSC. We included a subgroup of 18 patients with persistent subretinal fluid (SRF) after photodynamic therapy (PDT). Assessment included visual acuity (VA), central retinal thickness (CRT) and resolution of SRF. ***Results:*** At the last follow-up (mean 5 months), 74% of patients responded to therapy. The CRT decreased after treatment (mean CRT –115 µm, $p < 0.001$) and VA improved (mean logMAR –0.06, $p = 0.039$). No laser burns were detected with any imaging modality. In the subgroup of patients resistant to PDT, 61% of patients responded to therapy with a decrease in CRT (mean CRT –75 µm, $p = 0.019$). ***Conclusions:*** The 577-nm SML is an effective treatment for cCSC even in patients without sufficient improvement after PDT.

Introduction

Central serous chorioretinopathy (CSC) is characterized by vision loss due to a serous detachment of the neurosensory retina [1]. Clinical evidence from multimodal imaging, such as choroidal congestion and thickening and hyperpermeability of the choroid, suggests that choroidal dysfunction is an important underlying cause for retinal pigment epithelium (RPE) dysfunction and subretinal fluid (SRF) leakage in CSC [2, 3]. Two main subtypes of CSC can be distinguished: acute and chronic CSC (cCSC). In acute CSC, the detachment is caused by a focal leak ('hot spot') in the RPE. The SRF usually resolves spontaneously within a few weeks, and visual acuity (VA) recovers to (near-) normal in acute CSC [4].

However, cCSC can lead to permanent structural damage and often pronounced loss of central vision [5–7]. These patients show irregular mildly atrophic RPE changes and choroidal abnormalities which often occur without a single focal 'hot spot' but with more diffuse leakage.

So far, there is no 'gold standard' treatment for CSC. For extrafoveal leakage, the conventional suprathreshold argon laser photocoagulation can be used, which can accelerate resolution of SRF [6, 8]. Potential side effects in-

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E-Mail karger@karger.com
www.karger.com/oph

Sascha Fauser
Department of Ophthalmology, University Hospital of Cologne
Kerpener Strasse 62
DE–50924 Cologne (Germany)
E-Mail sascha.fauser@uk-koeln.de

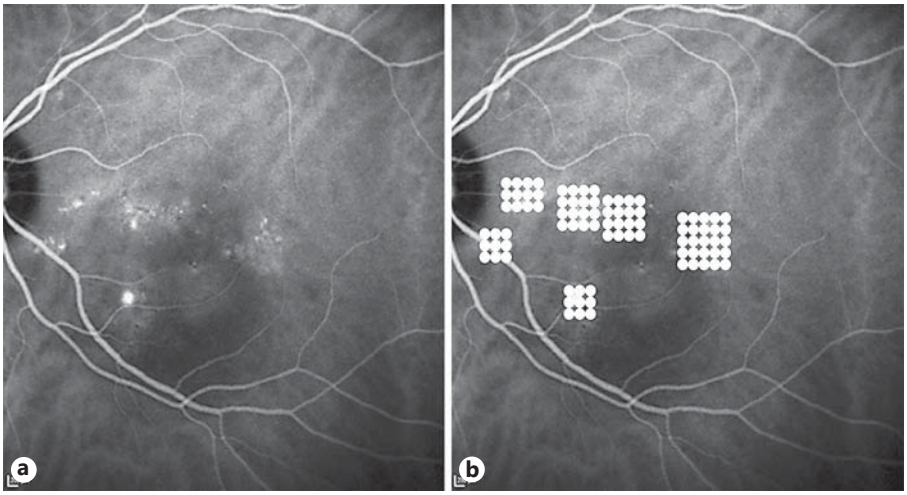

Fig. 1. a ICGA of a patient showing inkblot leakage pattern and diffuse RPE abnormalities typical for cCSC. **b** A schematic illustration of the micropulse laser treatment.

clude choroidal neovascularization [9] and a reduction of contrast sensitivity [10]. Furthermore, this laser treatment is not suitable for diffuse or central leakage as it causes scotomas. Another treatment option is photodynamic therapy (PDT) which can be applied even to juxtafoveal and subfoveal lesions. However, even when using reduced treatment settings, PDT also has potential side effects, such as RPE atrophy, choroidal neovascularization, choriocapillaris ischemia, and transient reduction of macular function [11–15].

Subthreshold micropulse laser (SML) treatment without any visible endpoint seems to be a promising alternative treatment strategy. In SML, energy is applied in very short laser pulses separated by enough time to allow heat dissipation and minimize thermal damage to the target tissue and its surrounding structures. It is assumed that retinal damage may not be needed to achieve a therapeutic effect [16]. After SML treatment, no laser spots on clinical examination can be detected. Several studies with a micropulse diode laser (810 nm) showed some efficacy in CSC patients with subfoveal and extrafoveal leakage sites [17–20].

We have now evaluated a new 577-nm micropulse laser which potentially allows a better titration of laser power as the individual threshold can be calibrated in the micropulse mode in the more peripheral retina as the power can be increased high enough to produce visible burns. This may allow a more effective treatment while maintaining subthreshold treatment. In this study, we retrospectively reviewed the effect of 577-nm SML treatment in patients with cCSC.

Patients and Methods

Data of patients treated with the Supra Scan 577-nm laser (Quantel Medical, Cedex, France) for cCSC were retrospectively analyzed. The diagnosis of cCSC with multimodal imaging was based on an extensive ophthalmologic examination, including fundoscopy, spectral domain optical coherence tomography (SD-OCT), fluorescein angiography (FA), and indocyanine green angiography (ICGA) (Spectralis, Heidelberg Engineering, Heidelberg, Germany). The definition of cCSC used in this study was based on the currently available literature, taking the following characteristics into account (all had to be present): serous SRF on SD-OCT, ≥1 areas of multifocal diffuse leakage on FA, and corresponding hyperfluorescence on ICGA, as described previously [21]. Patients with evidence of other retinal diagnoses, such as choroidal neovascularization or polypoidal choroidal vasculopathy, were excluded.

If both eyes of a patient were treated, only one randomly chosen eye was included in this analysis. We included patients with persistent SRF for at least 6 weeks who were treated with SML between November 2013 and December 2014. Patients with previous PDT treatments were included as long as the last treatment was more than 3 months prior to SML. Laser spots were applied with the Area Centralis contact lens (laser spot magnification ×0.94; Volk Optical Inc., Mentor, Ohio, USA). Standardized treatment parameters were used. The spot size was 160 μm, the exposure time 0.2 s, and a duty cycle of 5% was used. We chose a duty cycle of 5% because this allows for the heat production time to be shorter than the thermal relaxation time for the space between the RPE and the neural retina, which results in axial confinement of the increase in heat at the RPE [22].

To achieve a confluent laser treatment, the multispot mode, without spacing between the spots, was chosen (fig. 1). The individual power for the patient was titrated at a normal area of the retina, near the affected area in the monospot micropulse mode. The power titration was started at 700 mW and then gradually increased until a just visible burn was seen. When this threshold was reached, the power was reduced by 50%. With this power, the SML treatment of the hyperfluorescent areas on mid-phase ICGA and

the corresponding 'hot spots' on mid-phase FA was performed. The treatment outcome was evaluated using the best-corrected VA (BCVA), central retinal thickness (CRT) and resolution of SRF.

The CRT was measured using the automated segmentation program of the Heidelberg Eye Explorer software. All scans were checked for correct segmentation and correct positioning of the scan on the fovea and, if necessary, manually adjusted. The existence of SRF was assessed in the volume scans.

Statistical Analysis

SPSS (IBM SPSS Statistics, version 22) was used for the statistical analysis. The VA and the CRT before and after SML were compared using the Wilcoxon signed-rank test. The Spearman correlation coefficient was used to evaluate the correlation between the gain in BCVA and the reduction in CRT after SML treatment. Kaplan-Meier curves were calculated for morphological and functional response.

Results

Thirty-eight eyes of 38 consecutive patients (29 men and 9 women) were included in the analysis. The mean age of the patients was 51 years (range 32–69). The mean duration of disease before SML treatment was 4 years (range 4 months to 19 years).

In this study, 17 eyes received one SML treatment, 15 eyes two, and 6 eyes three SML treatments. BCVA at baseline was 0.36 (SD ±0.24) mean logarithm of the minimum angle of resolution (logMAR). CRT was 402 (SD ±139 μm). The mean follow-up after the first SML treatment was 5.0 months (SD ±3.7).

Treatment Outcome

At 6 weeks, in 5 out of 38 eyes (13%), the SRF had disappeared completely and in 19 eyes (50%), the SRF was reduced but had not completely disappeared. Fourteen eyes (37%) showed no improvement in SRF. The CRT decreased significantly 6 weeks after treatment (mean CRT before SML: 402 ± 139 μm, after SML: 309 ± 86 μm, $p < 0.001$), but BCVA showed no significant increase (mean logMAR before: 0.36 ± 0.24, after SML: 0.33 ± 0.24).

At the 3-month visit, in 7 out of 23 eyes (30%), the SRF had disappeared completely, and in 13 eyes (57%), the amount of SRF was reduced. In 3 eyes (13%), the amount of SRF increased. The CRT decreased significantly (mean CRT before SML: 410 ± 155 μm, after SML: 263 ± 57 μm, $p < 0.001$). BCVA showed no significant improvement (mean logMAR before: 0.33 ± 0.27, after SML: 0.27 ± 0.26).

At the 6-month visit, 2 out of 14 eyes (14%) showed no SRF and 9 eyes (64%) showed less SRF. In 3 eyes (21%), the SRF increased. The CRT remained significantly decreased (mean CRT before SML: 496 ± 175 μm, after SML: 276 ± 46 μm, $p = 0.005$). BCVA showed no significant improvement (mean logMAR before: 0.36 ± 0.23, after SML: 0.29 ± 0.19).

At the last follow-up (5.0 ± 3.7 months after SML), in 9 eyes (24%) the SRF had disappeared completely, and in 19 eyes (50%) the SRF was reduced. Ten eyes (26%) showed no improvement. The CRT decreased significantly after treatment (mean CRT before SML: 402 ± 139 μm, after SML: 287 ± 75 μm, $p < 0.001$), and BCVA showed a significant increase (logMAR before: 0.36 ± 0.24, after SML: 0.30 ± 0.25, $p = 0.039$).

The BCVA improved in 17 out of 38 eyes (45%) by one or more lines (in 8 eyes by one line, in 5 eyes by two lines and in 4 eyes by three or more lines). Fourteen eyes (37%) maintained vision, and 7 eyes (18%) lost one or two lines (5 eyes one and 2 eyes two lines).

There was a significant correlation between the gain in BCVA and the reduction in CRT after SML treatment ($p = 0.036$). Kaplan-Meier curves were calculated for morphological response (improvement in CRT of at least 15 μm) and functional recovery (increase in BCVA of at least one line) (fig. 2). In most cases, the functional response set in early, while BCVA improved over a longer period of time.

Disease Recurrence

One eye with a complete resolution of SRF after 3 months had a recurrence 10 months after the initial treatment. Five eyes with persistent SRF 6 weeks after the first treatment showed a complete resolution of SRF after a second SML treatment and stayed dry until the last follow-up. Four eyes showed a complete resolution of SRF at the 6-week visit and stayed dry during the follow-up period of up to 8 months.

Pretreatment with PDT

The subgroup of patients who did not respond sufficiently to one or more half-dose PDT treatments in the past (n = 18) was analyzed. In this group, 2 eyes (11%) showed a complete resolution of SRF at the last follow-up, in 9 eyes (50%) the SRF was reduced, and 7 eyes (39%) showed no improvement. The CRT decreased significantly after treatment (mean CRT before SML: 357 ± 131 μm, after SML: 282 ± 54 μm, $p = 0.019$). BCVA showed no significant increase (mean logMAR before: 0.37 ± 0.20, after SML: 0.33 ± 0.19). The reduction in CRT was smaller (CRT: –75 ± 140 μm; BCVA: –0.03 ± 0.1 logMAR) than in the group of previously untreated patients (CRT:

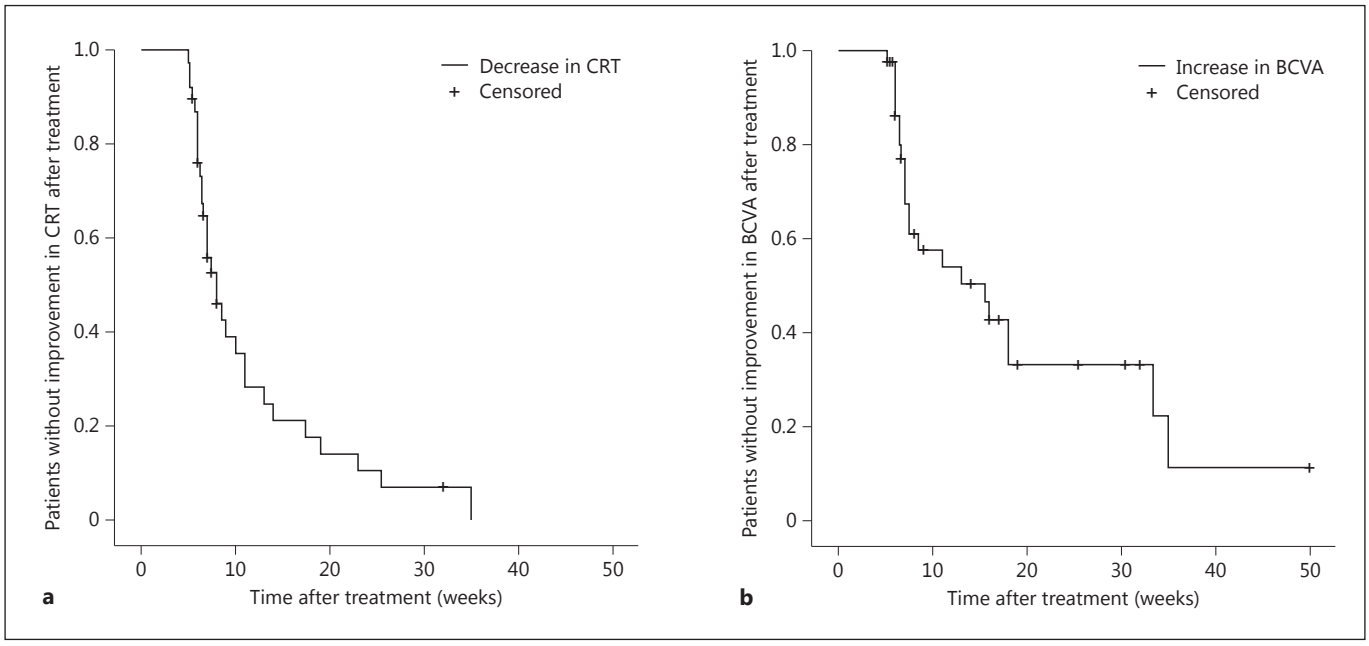

Fig. 2. Kaplan-Meier plots on treatment response after SML treatment. **a** Time point when patients showed a reduction in CRT of at least 15 μm. **b** Time point when patients showed an improvement in BCVA of at least 1 line.

–152 ± 144 μm; BCVA: –0.09 ± 0.2 logMAR), although the difference was not statistically significant.

Nonresponse to SML Treatment

In the group of patients who did not respond to the SML treatment, the average age was significantly higher than in the group of responders (mean age nonresponders: 56.0 years, SD ±8.7; responders: 47.9 years, SD ±7.8, p = 0.013). Regarding the disease duration and number of leakage points, there was no significant difference between the two groups (p = 0.476 and p = 0.489, respectively). However, a diffuse RPE decompensation with or without additional point source leakage was found in 100% of the nonresponders, whereas this was found in only 52% of the responders (p = 0.009).

Safety

No laser spots were detected after treatment by biomicroscopy, SD-OCT, fundus autofluorescence, infrared reflectance image, or FA and ICGA. Patients with up to three SML treatments also did not show any structural laser damage. We only detected laser spots from the titration procedure in the retinal periphery by increased autofluorescence.

Discussion

In this study, SML treatment with a 577-nm laser was associated with disappearance or a significant reduction of SRF in 75% of patients with cCSC. As all patients had at least 4 months of persistent SRF, the effect was likely attributable to the laser treatment effect and not to a spontaneous resolution of fluid in most cases. Overall, we saw a small improvement of BCVA that was correlated with the reduction in CRT. However, our cohort had an often long-standing history of CSC of up to 19 years with possibly permanent structural damage that precluded marked visual improvement. However, even patients without BCVA improvement will probably benefit from a resolution of the serous neuroretinal detachment because of a prevention of further retinal atrophy and stabilization of visual function [23]. It is also important to note that even severe, long-standing cases could show a reduction or resolution of SRF. Nonresponse was associated with a diffuse RPE decompensation and a higher age but not with the duration of disease. A resolution or reduction of SRF may still be achieved with SML therapy in cCSC patients who did not respond to prior half-dose PDT treatments. This does not mean that PDT was inferior per se but that some patients might be more suitable

to either PDT or SML or that there may even be a synergistic effect when combining both methods. Kaplan-Meier analysis showed that morphological improvements tend to set in earlier than functional recovery.

In previous studies with 577-nm SML, a complete resolution in 33–75% and at least a partial resolution in 100% of patients with cCSC were reported [24, 25]. However, these studies used other inclusion criteria and some patients with more acute CSC who are more inclined to dry up spontaneously. In our study, 24% of patients dried up completely and 75% showed at least a partial resolution of fluid. However, this less favorable outcome is possibly due to the severity of the disease in our cohort with a phenotype of diffuse leakage, a very long-standing disease, or being refractory to previous treatment with PDT.

As there is no visible endpoint in SML treatment, there is a risk of undertreatment. Therefore, we used confluent treatment of the affected retinal and choroidal area and individually adjusted the laser power by the titration procedure described above. Despite this, several patients needed a repetition of the SML which then further decreased SRF. Nevertheless, even after three treatments, no structural laser damage was seen. Overall, we did not observe any adverse events in the whole cohort. Treatment very close to the fovea was also safe. This indicates that 577-nm SML treatment can be performed safely and repeatedly, although long-term follow-up studies are required to confirm this on the long run.

Although there seems to be a clear treatment effect of SML therapy in our retrospective case series, only a minority of eyes (24%) had a complete resolution of SRF at the final follow-up, but another 51% of eyes showed a significant reduction of SRF accumulation. Our data indicate that SML generally achieves its gradual effect on SRF reduction and resolution over several months, and it is unclear to what extent cCSC patients benefit visually from SRF reduction without SRF resolution. Based on the available largely retrospective literature on half-dose PDT and other PDT strategies using reduced settings, PDT may be able to achieve a faster and a complete resolution in a larger proportion (60–100%) of cCSC patients [13, 14]. However, there are benefits of SML treatment over PDT treatment in CSC. Unlike PDT, which uses the intravenously administered light-activated verteporfin, there is no need after SML treatment to be protected from bright light in the first days after treatment. In addition, choroidal neovascularization and RPE atrophy have been described in a small subgroup of PDT-treated CSC patients [14, 15] but have thus far not been described in SML. It is generally assumed that more than two PDT treatments, even when using reduced dosage, fluence, or time settings, carry a higher risk of complications such as RPE atrophy. SML treatment presumably can be repeated more often in a safe manner. This difference is possibly due to the fact that the effect of PDT treatment leans on a suprathreshold effect on the choriocapillaris that may result in structural changes, whereas SML treatment is by definition subthreshold and is aimed at the RPE. However, the precise mechanisms of the possible therapeutic effect of SML are unclear. SML treatment using 577-nm wavelength pulses is a relatively new technique, and SML treatment using 810-nm wavelength has been previously described as a possible treatment in CSC [17–20]. It is unclear which SML wavelength is more effective and/or safer. In a rabbit study, similar duty cycle-dependent histological effects were seen in 810- and 532-nm SML strategies [26].

Limitations of the present study are the absence of a control group and a relatively short follow-up time with nonstandardized follow-up periods because of the retrospective nature of the study. Without a randomized trial including a control group, we cannot rule out a spontaneous resolution of SRF after the SML, although the long-standing disease in all patients makes this possibility less likely. In addition, the lack of a visible endpoint after SML treatment complicates decision making in choosing the optimal treatment settings to achieve the maximal effect. Treatment settings with this relatively new 577-nm SML laser modality should therefore be subject of further study.

In conclusion, this case series indicates that 577-nm SML treatment can be an effective and safe treatment for cCSC with persistent SRF, even in a subgroup of patients who did not respond to prior PDT treatment. As there are no known side effects and no clearly detectable structural damage after SML, early SML treatment could be considered and might help to avoid permanent structural damage and lasting visual impairment in cCSC patients. The role of SML treatment in CSC should be further examined because multicenter randomized controlled treatment trials on this topic are lacking thus far. We are currently performing such a multicenter prospective randomized controlled trial comparing half-dose PDT with high-density SML as a primary treatment for cCSC (EudraCT No. 2012-004555-36, NCT01797861).

Disclosure Statement

The authors have no proprietary or commercial interest in any materials discussed in this article.

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