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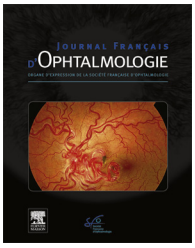

ORIGINAL ARTICLE

Subthreshold nanosecond laser therapy for chronic central serous chorioretinopathy: A prospective study

Thérapie au subthreshold nanolaser *pour la choriorétinopathie centrale séreuse chronique : une étude prospective*

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KEYWORDS
Central serous chorioretinopathy ;
Pachychoroid ;
Subthreshold nanosecond laser ;
Subretinal fluid ;
Microperimetry

Summary
Purpose. — To investigate the morphologic and functional outcomes of nanosecond subthreshold (ST) laser treatment for patients with chronic central serous chorioretinopathy (CSC).
Methods. — In this prospective study, 44 patients were treated with the ST nanosecond laser with a follow-up period of 12 months. All target variables were measured at 1, 3, 6 and 12 months after the first laser treatment.
Results. — This study showed a significant improvement in macular sensitivity (MS), a significant reduction in central macular thickness (CMT) as well as a significant reduction in subretinal fluid height (SRF) after 3 months of treatment. The subfoveal choroidal thickness (SFCT) was significantly reduced after 12 months of treatment. However, the best-corrected visual acuity (BCVA) (logMAR) did not change significantly at any time during the study. A high proportion of patients (85%) showed complete resolution of SRF after 12 months, indicating a positive response to treatment in the majority of our patients.

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Conclusion. — This study showed statistically significant functional improvement in MS as well as significant anatomical reduction in CMT, SFCT and SRF height in CSC patients treated with ST nanosecond laser therapy. Patients with higher SRF at baseline required repeated laser treatments to achieve complete resolution of the SRF.

MOTS CLÉS
Choriorétinopathie centrale séreuse ;
Pachychoroïde ;
Subthreshold nanolaser ;
Liquide sous-rétinien ;
Micropérimetrie

Résumé
Objectif. — Étudier les résultats morphologiques et fonctionnels du traitement au *subthreshold* (ST) *nanolaser* pour les patients atteints de choriorétinopathie centrale séreuse chronique (CCS).
Méthodes. — Dans cette étude prospective, 44 patients ont été traités au ST *nanolaser* avec une période de suivi de 12 mois. Toutes les variables ont été mesurées à 1, 3, 6 et 12 mois après le premier traitement au laser.
Résultats. — Cette étude a démontré une amélioration significative de la sensibilité maculaire (SM) et une réduction significative de l'épaisseur maculaire centrale (EMC), ainsi que de la hauteur du liquide sous-rétinien (LSR) après 3 mois de traitement. L'épaisseur choroïdienne sous-fovéale (ECSF) n'a été significativement réduite qu'après 12 mois de traitement. Cependant, la meilleure acuité visuelle corrigée (MAVC) (logMAR) n'a pas changé de manière significative durant l'étude. La majorité des patients (85 %) a montré une résolution complète du LSR après 12 mois, ce qui indique une réponse positive au traitement.
Conclusion. — Cette étude a démontré une amélioration statistiquement significative de la SM ainsi qu'une réduction significative de l'EMT, de l'ECSF et de la hauteur du LSR chez les patients atteints de CCS traités au ST *nanolaser*. Les patients présentant un LSR plus élevé au départ ont dû subir plusieurs traitements pour obtenir une résolution complète du LSR.

Introduction

Central serous chorioretinopathy (CSC) usually affects young men with a peak in the third or fourth decade of life. Typical symptoms are metamorphopsia, micropsia, mild dyschromatopsia, increasing hyperopia and decreased contrast sensitivity. CSC is characterized by serous detachment of the retinal pigment epithelium (RPE) and/or subretinal fluid (SRF) accumulation with variable photoreceptor (PR) degeneration. Up to 30—50% of cases of acute CSC recur and may progress to a chronic form with RPE atrophy associated with variable PR degeneration or macular neovascularisation (MNV) leading to permanent visual loss [1—3].

The continued development of choroidal imaging has led to a better understanding of many chorioretinal disorders and to a new spectrum of pachychoroid-related macular disorders defined by abnormally increased choroidal thickness as well as choroidal vascular hyperpermeability, dilation of the outer choroidal veins and atrophy of the internal choroidal layers. Identified risk factors for CSC include untreated hypertension, pregnancy, psychosomatic pathologies (type A behavior, stress) and *Helicobacter pylori* infections. Exogenous corticosteroid use and/or endogenous hypercortisolism also appear to play a key role in the pathophysiology of CSC [2—9].

To date, no clear consensus has been reached for the treatment and management of CSC, but several treatment options have been proposed, such as aldosterone-receptor antagonists, verteporfin half-dose photodynamic therapy (PDT) and lastly the micropulse laser including the subthreshold (ST) nanosecond laser treatment. Over the past few years, this minimally invasive laser treatment, using low-energy ultrashort pulses, has gained popularity and has been commonly used as an alternative treatment for macular oedema, such as diabetic macular oedema, retinal vein occlusion or CSC. This was advisable, especially considering that verteporfin had not been available in Germany for some months [10—12].

Purpose of this prospective study was to investigate the morphological and functional outcome of the ST nanosecond laser treatment for patients with chronic CSC.

Patients and methods

Design

This prospective, multicenter, non-randomized study was conducted at the department of Ophthalmology at Saarland University Medical Center in Homburg/Saar (UKS) as well as the ophthalmological practice Breyer, Kaymak, Klabe (Internationale Innovative Ophthalmochirurgie) in Dusseldorf, Germany. Ethical approval for this study was obtained

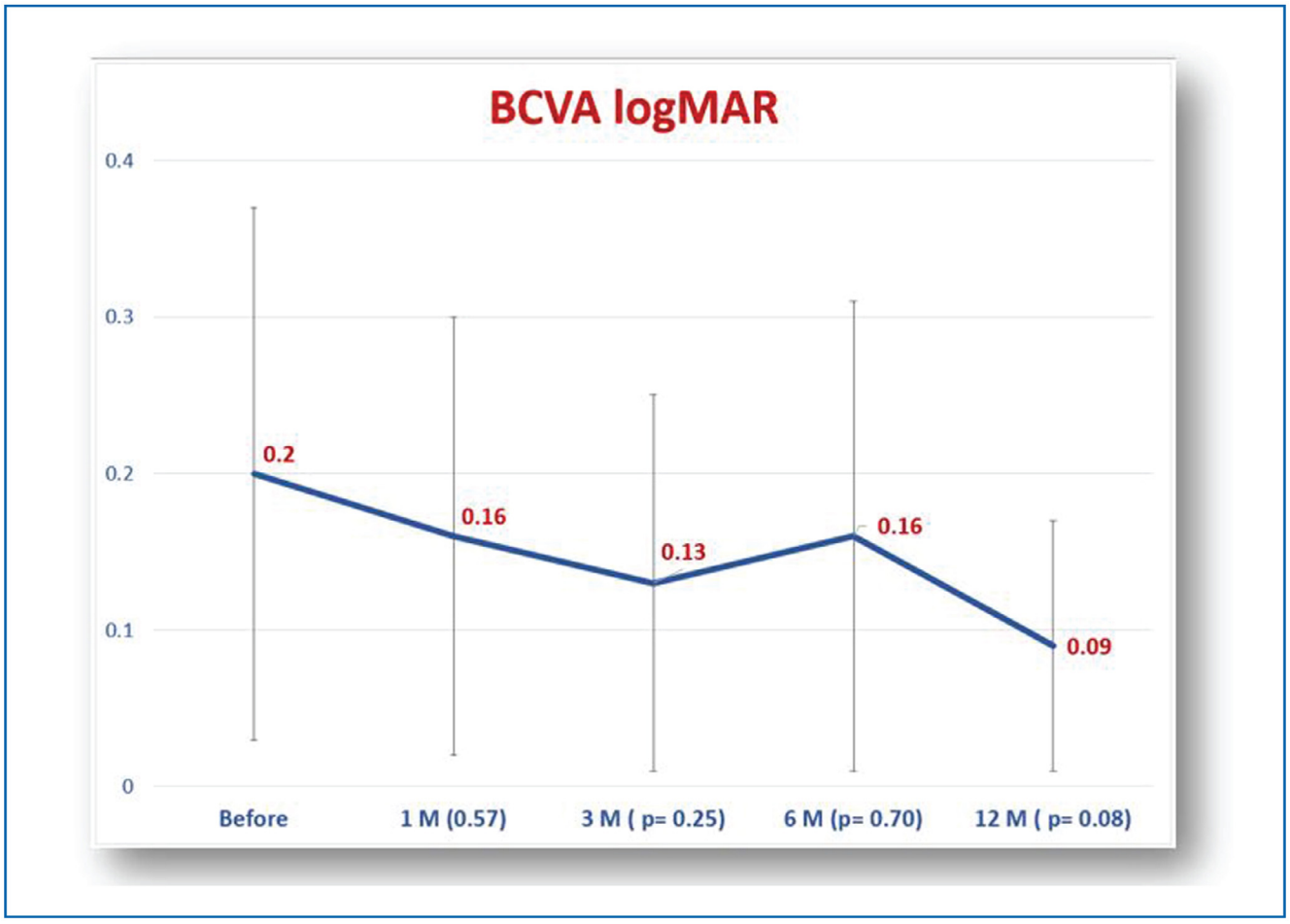

Figure 1. Best corrected visual acuity (BCVA) after 1, 3, 6 and 12 months of treatment. Results are given as means ± standard deviation; *P*-value refers to statistical differences between baseline values, values after 1, 3, 6 and 12 months of treatment.

from the ethics committee Ärztekammer des Saarlandes (reference number 196/19).

Patients

Forty-four eyes of 44 patients with CSC were recruited in the study and received laser treatment between 2019 and 2021. All patients were diagnosed with chronic CSC using ophthalmoscopy, spectral-domain optical coherence tomography (SD-OCT), fundus autofluorescence images and fluorescein- and indocyanine green angiography (FA, ICGA). FA images were used to determine the integrity of RPE and provide information as to whether the disease had already taken a chronic course. Patients with chronic CSC were defined according to the guidelines of the German Society of Ophthalmology by the presence of flat RPE changes of varying extent with associated photoreceptor degeneration [1]. The combination of SD-OCT, FA, ICGA, and OCT angiography (OCT-A) was used to detect MNV [1].

Exclusion criteria were the presence of any other macular disease (including age-related macular degeneration, diabetic retinopathy, retinal vessel occlusion), high myopia (> −6 diopters or axial length > 26 mm), history of treatment with intravitreal anti-vascular endothelial growth factor (anti-VEGF) or laser retinal therapy, history of treatment with local or systemic corticosteroids within the past 6 months; pregnant or lactating women; allergy to fluorescein; other serious somatic or mental illnesses that may preclude regular participation in the study; surgery planned within the next 12 months; and patients under 18 years of age.

Study protocol

All patient medical records, imaging data and target variables were reviewed at baseline, 1, 3, 6 and 12 months after the first laser treatment.

Main outcome measures included:

- best-corrected visual acuity (BCVA) as measured on a Snellen decimal scale and converted to logMAR scale;
- presence of metamorphopsia (Amsler grid-test);
- macular sensitivity (MS) measured by microperimetry using the MAIA device (CENTERVUE S.P.A., Padua, Italy);
- height of subretinal fluid (SRF) as measured manually by Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany) and defined as the vertical distance (μm) from the hyperreflective line of the RPE to the hyperreflective line of the inner edge of the detached retina at the fovea;
- central macular thickness (CMT) as measured by Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany) and defined as the mean retinal thickness (μm) between

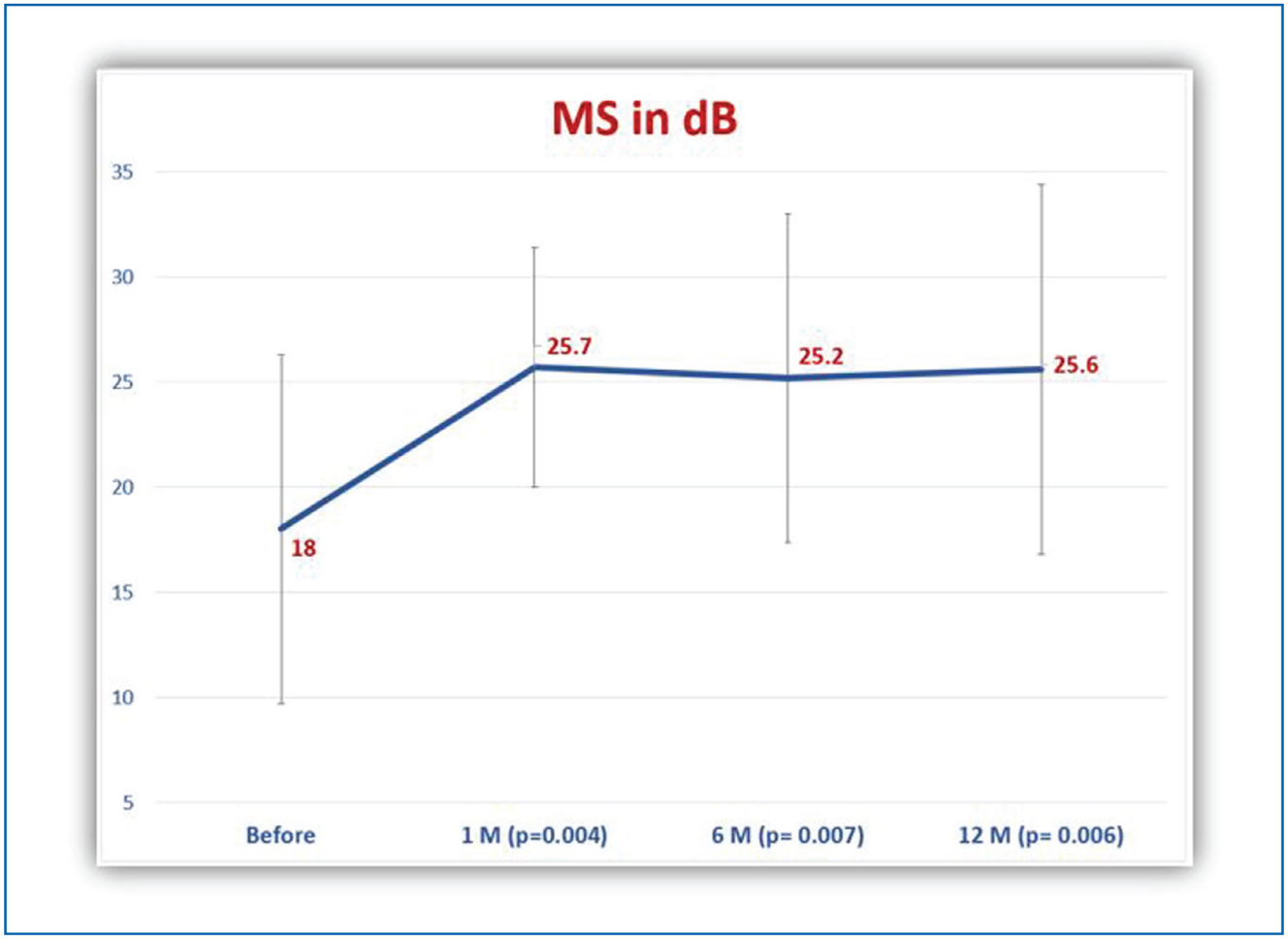

Figure 2. Mean macular sensitivity (MS) 1, 6 and 12 months of treatment. Results are given as means ± standard deviation; *P*-value refers to statistical differences between baseline values, values after 1, 6 and 12 months of treatment.

the internal limiting membrane (ILM) and the basement membrane of Bruch (BM) in the central 1 mm of the fovea;
- subfoveal choroidal thickness (SFCT) as measured by the Enhanced Depth Imaging Mode (Spectralis EDI SD-OCT; Heidelberg Engineering, Heidelberg, Germany);
- exclusion of MNV performed by OCT angiography (OCT-A) (CIRRUS HD 5000, Carl Zeiss Meditec, Jena, Germany);
- FA and ICGA (Spectralis HRA2 Heidelberg Engineering, Heidelberg, Germany) were performed at baseline and 12 months after the first laser treatment;
- poor response was defined as incomplete resolution of SRF after the first the subthreshold (ST) nanosecond laser treatment.

Patients were divided into two study groups: a responder group and a low-responder group based on their response to treatment, which required multiple laser treatments to achieve complete resolution of SRF. Comparisons between the responder and low-responder groups were performed to identify factors predictive of treatment response. We also examined the proportion of eyes that achieved complete resolution of SRF.

Treatment protocol

All 44 patients were treated with the 2RT®-Laser (RT: Retinal Rejuvenation) (Ellex Medical Laser Ltd., Mawson Lakes, Australia) using a maximal energy of 0.18 mJ and pulse duration of 3 ns. A total of 30—40 spots with a spot size of 400 μm were applied, depending on the area of SRF. Laser spots were administrated across the entire SRF region. Laser treatment was repeated up to 3 times depending on the clinical response as well as in cases of recurrence. The potential benefits and risks of treatment were discussed with all patients and informed consent was obtained.

Statistical analysis

Comparisons between variables at baseline, 1, 3, 6 and 12 months were performed using a generalized linear model. Comparison between groups were done with Mann-Whitney *U*-test, *t*-test and Chi^2 test were appropriate. Data were presented as mean ± standard deviation. Results were considered statistically significant if *P*-values were ≤ 0.05. Data were analysed using SPSS 27.0 for windows (SPSS, Inc., Chicago, IL).

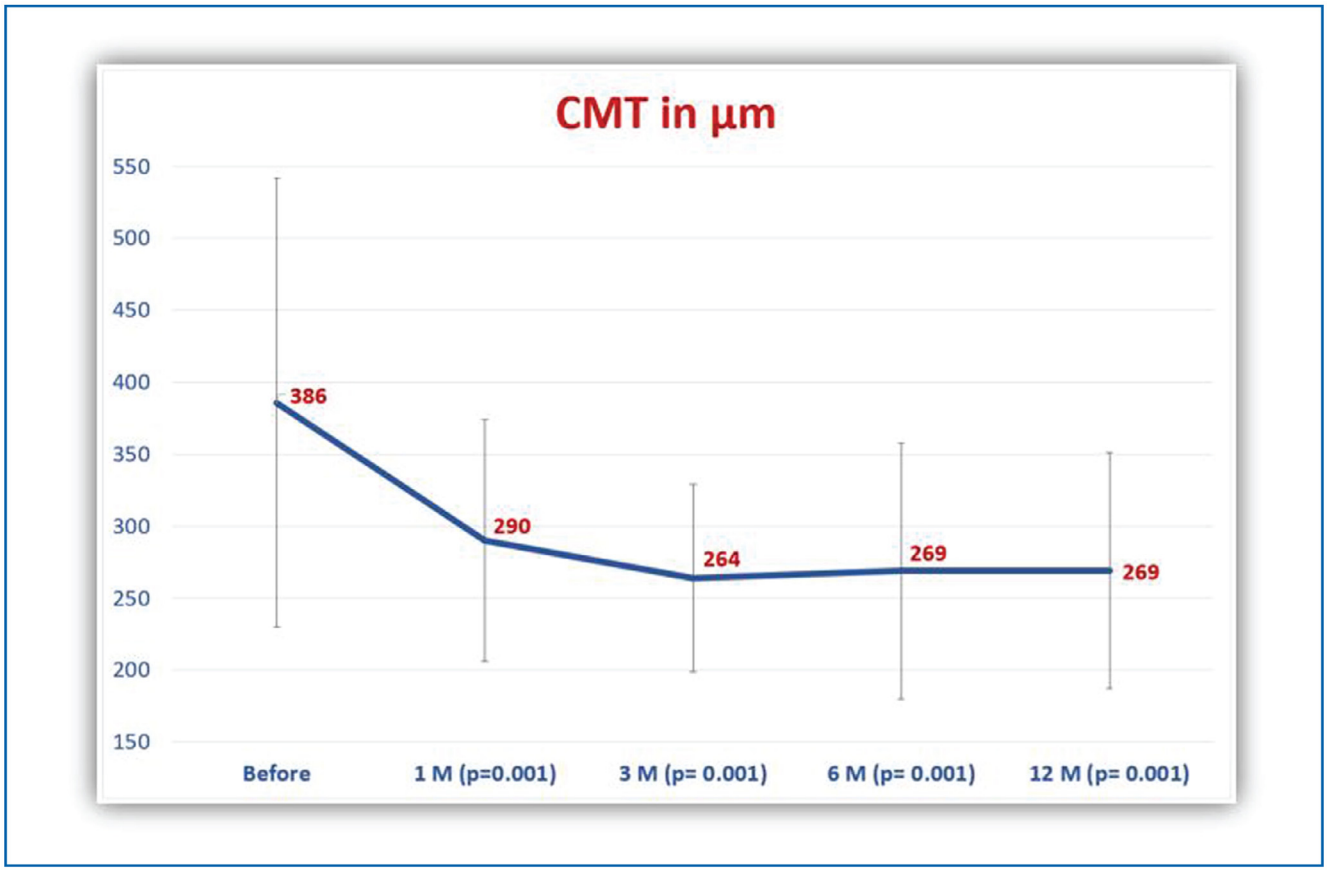

Figure 3. Central macular thickness (CMT) after 1, 3, 6 and 12 months of treatment. Results are given as means ± standard deviation; *P*-value refers to statistical differences between baseline values, values after 1, 3, 6 and 12 months of treatment.

Results

Mean age of patients was 48.4 ± 2.7 years. Only two (4%) patients were female.

Mean BCVA (logMAR) improved from 0.2 ± 0.03 to 0.16 ± 0.03 at 1 month ($P = 0.57$), to 0.13 ± 0.03 at 3 months ($P = 0.25$), to 0.16 ± 0.03 at 6 months ($P = 0.70$) and to 0.09 ± 0.04 at 12 months ($P = 0.08$) (Fig. 1).

Mean MS (dB) improved significantly from 18 ± 8.3 to 25.7 ± 5.7 at 1 month ($P = 0.004$), to 25.2 ± 7.8 at 6 months ($P = 0.007$) and to 25.6 ± 8.8 at 12 months ($P = 0.006$) (Fig. 2).

Mean CMT (µm) decreased significantly from 386 ± 156 µm to 290 ± 84 µm at 1 month ($P = 0.001$), to 264 ± 65 µm at 3 months ($P = 0.001$), to 269 ± 89 µm at 6 months ($P = 0.001$) and to 269 ± 82 at 12 months ($P = 0.001$) (Fig. 3).

Mean height of SRF (µm) decreased significantly from 176 ± 150 µm to 67 ± 86 µm at 1 month ($P = 0.001$), to 36 ± 57 µm at 3 months ($P = 0.001$), to 60 ± 91 µm at 6 months ($P = 0.001$) and to 41 ± 71 µm at 12 months ($P = 0.001$) (Fig. 4).

There was a significantly negative correlation between height of SRF and MS ($P < 0.0001$).

Mean SFCT (µm) decreased from 358 ± 62 µm to 332 ± 67 µm at 1 month ($P = 0.09$), to 320 ± 56 µm at 3 months ($P = 0.17$), to 312 ± 62 µm at 6 months ($P = 0.06$), and to 318 ± 65 µm at 12 months ($P = 0.02$) (Fig. 5).

Twenty-two patients (50%) needed more than one laser session and were considered low-responders. Laser treatment was repeated up to three times with an average of 1.85 laser sessions. There were no statistical significant differences between the responder and low-responder group in age, sex ratio, BCVA, SFCT and CMT at baseline. Height of the SRF was the only statistically significant factor ($P = 0.01$) associated with a lower treatment response (Table 1).

Complete resolution of SRF was achieved in 27 patients after 3 months (61%), 31 patients at 6 months (70%) and 37 patients at 12 months (85%). No patients developed secondary MNV during the study period.

Discussion

According to the recommendations of the DOG (Deutschen Ophthalmologischen Gesellschaft) and BVA (Berufsverband der Augenärzte Deutschlands), patients with acute CSC should not be treated within the first four months of disease onset, as SRF tends to regress spontaneously [1]. However, CSC patients are usually young, professionally active and complain about a decreased vision-related quality of life. In addition, the risk of clinical sequelae with irreversible photoreceptor (PR) damage increases with duration and extent of SRF, thus a treatment approach to accelerate the natural remission of the disease and prevent recurrences is

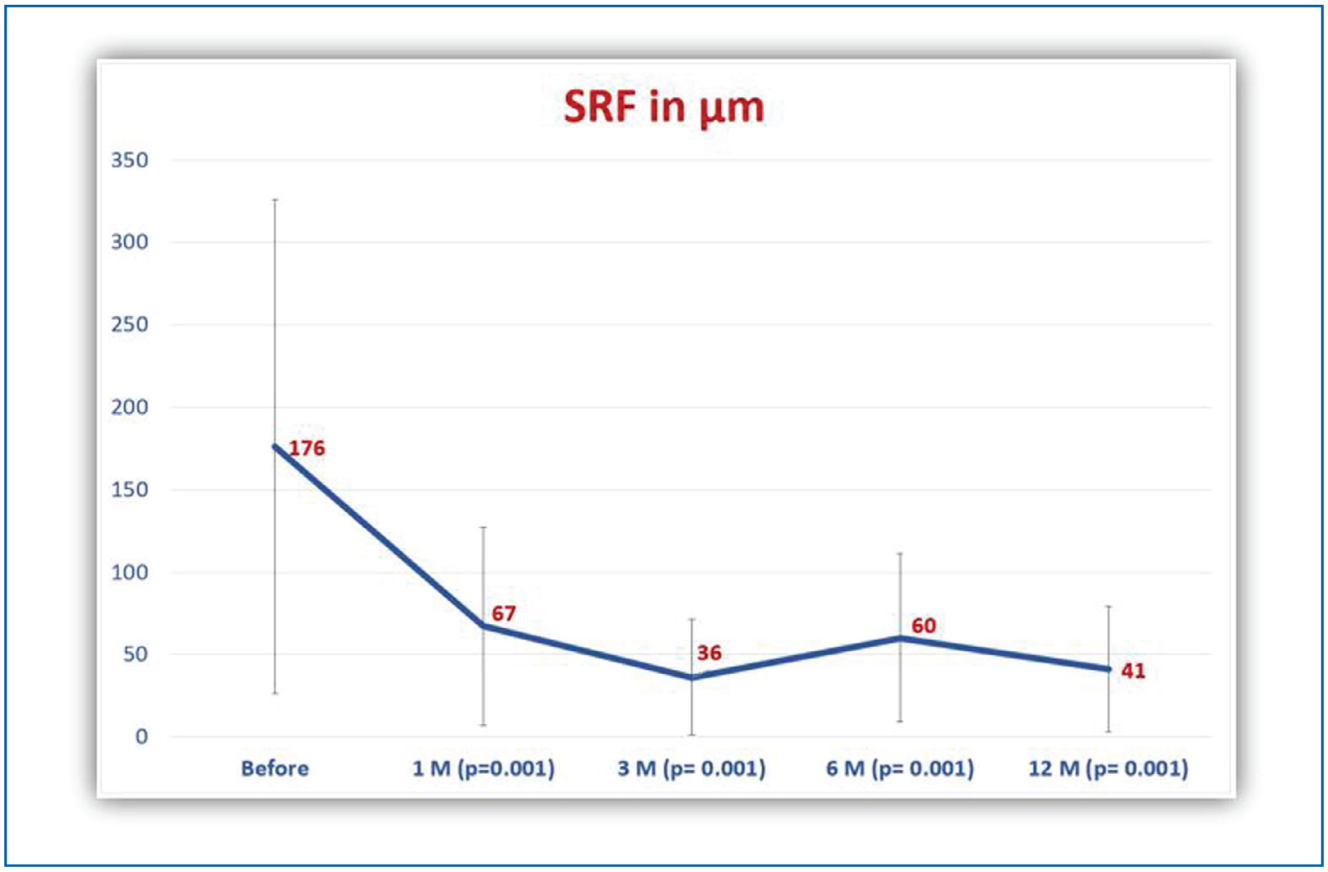

Figure 4. Height of subretinal fluid (SRF) after 1, 3, 6 and 12 months of treatment. Results are given as means ± standard deviation; *P*-value refers to statistical differences between baseline values, values after 1, 3, 6 and 12 months of treatment.

Table 1 Predictive factors of the treatment response for the subthreshold nanosecond laser.

Baseline characteristics (mean ± SD)	Response ($n = 22$)	Low response ($n = 22$)	*P*-value
BCVA (logMar)	0.18 ± 0.2	0.17 ± 0.15	0.99
MS	16.4 ± 9.2	19.6 ± 7.2	0.32
SFCT	360 ± 54	356 ± 73	0.87
SRF	155 ± 190	166 ± 94	0.01
CMT	367 ± 195	406 ± 105	0.41
Age	48.4 ± 12	49.1 ± 10	0.83

BCVA: best-corrected visual acuity; MS: mean macular sensitivity; SFCT: mean subfoveal choroidal thickness; SRF: height of subretinal fluid; CMT: mean macular thickness. Results are given as means ± standard deviation; *P*-value refers to statistical differences between responder and low-responder group. Comparison between the baseline characteristics of the responder and low-responder group.

advisable. However, due to the favourable visual prognosis of CSC patients, the treatment modalities chosen must have a favourable safety profile [10,11].

Because of the lack of consensus on a classification system for CSC, their high clinical variability, high rates of spontaneous resolution, and the lack of large prospective randomized controlled studies on the subject, defining an optimal treatment for patients with CSC is a challenge [11]. The only large, prospective randomised controlled treatment trial for the treatment of chronic CSC conducted is the PLACE trial comparing the half-dose PDT laser versus the high-density ST micropulse laser treatment [12]. They concluded that the half-dose PDT laser is superior to ST micropulse laser for treating chronic CSC, leading to a significantly higher proportion of patients with complete resolution of SRF and functional improvement. Half-dose PDT has emerged as the treatment of choice in many centres worldwide due to its favourable results and safety profile. Nonetheless, as noted above, some regions of Europe have not had reliable access to verteporfin (Visudyne, Novartis, Basel, Switzerland) for nearly two years, necessitating the use of other treatment modalities.

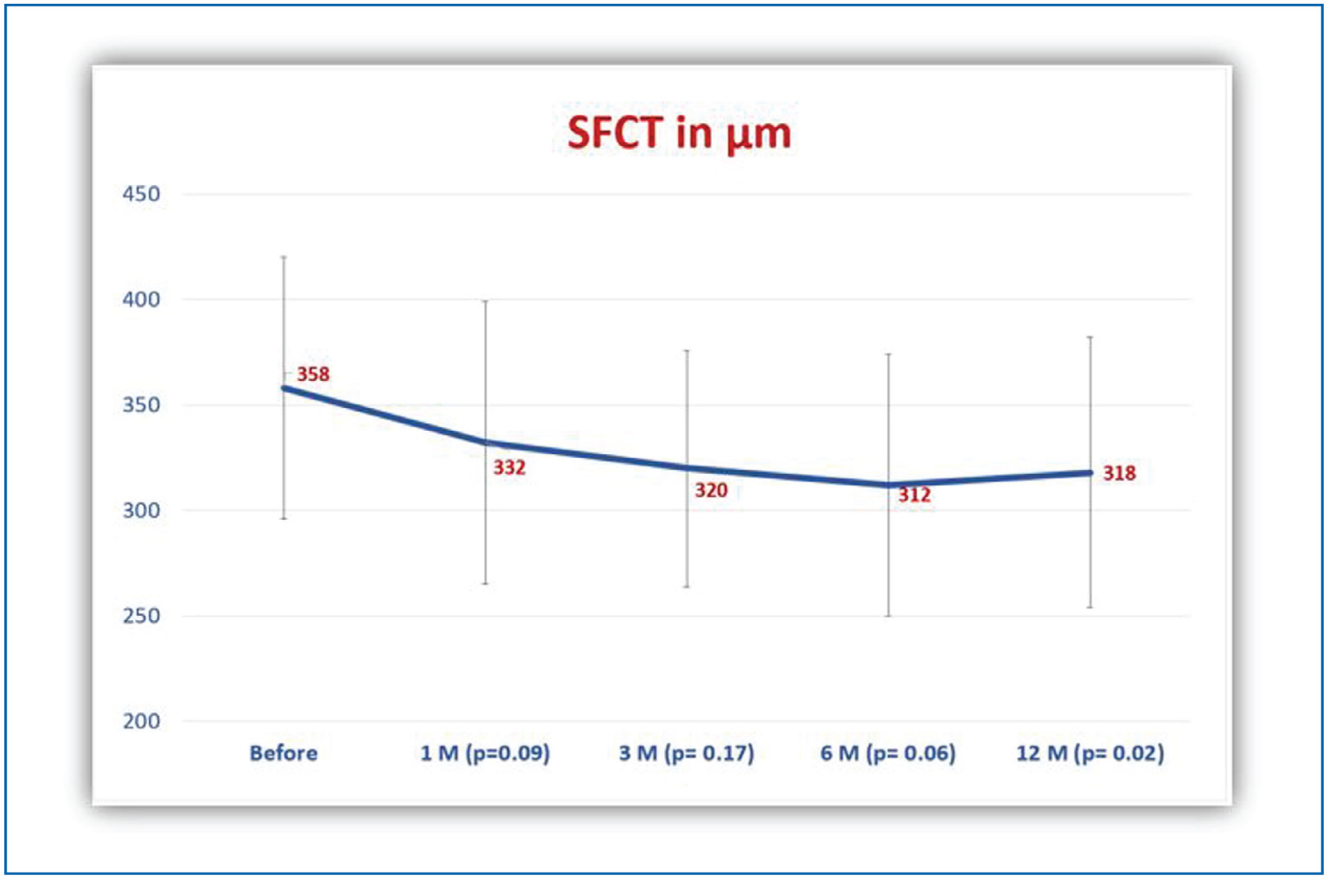

Figure 5. Subfoveal choroidal thickness (SFCT) after 1, 6 and 12 months of treatment. Results are given as means ± standard deviation; *P*-value refers to statistical differences between baseline values, values after 1, 6 and 12 months of treatment.

The goal of the ST nanosecond laser is to provide a safe, minimally invasive therapeutic alternative to restore an intact blood-retinal barrier, without damaging the adjacent retina. The ST nanosecond laser selectively stimulate RPE cell apoptosis, migration and proliferation in order to replace altered RPE cells, recover RPE pump function and therefore stimulate resorption of SRF. This ultimately leads to restoration of an intact outer blood-retinal barrier, without damaging the neural retina, PR or choroid. Due to the short laser pulses, causing heat dissipation, only the melanin granules of the melanosomes in the RPE cells absorb some of the supplied energy and induce RPE apoptosis, while preserving adjacent PR. Moreover, due to its safety profile the ST nanosecond laser treatment can directly be applied on sub- or juxtafoveolar retinal fluid [10,11].

Few studies have been published on the topic debating the treatment modalities and effectivity of the subthreshold laser treatment, but most are retrospective, small cohort, non-randomized studies with distinct inclusion und exclusion criteria, clinical definitions, study endpoints as well as other laser devices [10—13].

The only large, prospective randomised controlled treatment trial for the treatment of chronic CSC is the PLACE trial comparing the half-dose PDT laser versus the high-density ST micropulse laser treatment. The authors concluded that the half-dose PDT laser is superior to ST micropulse laser for treating chronic CSC, leading to a significantly higher proportion of patients with complete resolution of SRF and functional improvement [12]. Half-dose PDT has emerged as the treatment of choice in many centers worldwide due to its favorable results and safety profile. Nonetheless, as noted above, some regions of Europe have not had reliable access to verteporfin (Visudyne, Novartis, Basel, Switzerland) for nearly two years, necessitating the use of other treatment modalities. Finally, it is important to note, that the micropulse laser protocol used in our study diverges from the one used in the PLACE trial, which points out to the difficulty to compare results between the few available studies using laser therapie to treat patients with CSC.

In 2019, S. Funk et al. investigated the efficacy and safety of the nanosecond laser treatment in 23 acute CSC patients in a retrospective study. They showed a statistically significant improvement of SRF height with increase in MS [10]. In this present study, the nanosecond laser therapy also seems to be an effective and safe treatment method for patients with chronic CSC, but repetitive laser treatments were needed for patients with higher SRF at baseline. Mean MS increased significantly after 3 months, with no signs of iatrogenic PR damage. BVCA did not improve significantly during our study period. Nevertheless, CSC patients without PR damage usually present with a good baseline visual acuity and still complain about discommoding visual disturbances. In that regard, MS might be preferred as functional outcome compared to BCVA. This was supported by the negative correlation between SRF height and MS.

We compared the SFCT between the responder and low-responder group to discover if the SFCT was a potential parameter predictive of the treatment response or if it could be linked with active pathology. In our study mean SFCT decreased over the treatment period. This raises the question of whether choroidal thickness might only be a causal factor in CSC or could also be used as a sensitive predictor of treatment response (Table 1). However, no significant differences were found between the responder and low-responder group.

Limitations

The main limitations of our study were the lack of a control or comparison treatment group, the non-randomized nature of the study, the limited sample size, the need for repeated treatments, and the use of a single type of laser. Further prospective randomised studies with larger cohorts are needed to confirm our findings and further explore the predictors of response to treatment as well as the causes of recurrence.

Conclusions

This study showed statistically significant functional improvement in MS as well as significant anatomical reduction in CMT, SFCT and SRF height in CSC patients treated with ST nanosecond laser therapy. Patients with higher SRF at baseline required repeated laser treatments to achieve complete resolution of the SRF.

Ethical statement

Ethical approval for this study was obtained from the ethics committee Ärztekammer des Saarlandes (reference number 196/19).

Funding

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Disclosure of interest

The authors declare that they have no competing interest.

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