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Selective Retina Therapy in Acute and Chronic-Recurrent Central Serous Chorioretinopathy

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Key Words
Central serous chorioretinopathy · Chronic disease · Acute disease · Selective retina treatment · Subretinal fluid · Fluorescein angiography

Abstract
Purpose: Selective retina therapy (SRT), the confined laser heating and destruction of retinal pigment epithelial cells, has been shown to treat acute types of central serous chorioretinopathy (CSC) successfully without damaging the photoreceptors and thus avoiding laser-induced scotoma. However, a benefit of laser treatment for chronic forms of CSC is questionable. In this study, the efficacy of SRT by means of the previously used 1.7-µs and shorter 300-ns pulse duration was evaluated for both types of CSC, also considering re-treatment for nonresponders. ***Material and Methods:*** In a two-center trial, 26 patients were treated with SRT for acute (n = 10) and chronic-recurrent CSC (n = 16). All patients presented with subretinal fluid (SRF) in OCT and leakage in fluorescein angiography (FA). SRT was performed using a prototype SRT laser system (frequency-doubled Q-switched Nd:YLF-laser, wavelength 527 nm) with adjustable pulse duration. The following irradiation settings were used: a train of 30 laser pulses with a repetition rate of 100 Hz and pulse durations of 300 ns and 1.7 µs, pulse energy 120–200 µJ, retinal spot size 200 µm. Because SRT lesions are invisible, FA was always performed 1 h after treatment to demonstrate laser outcome (5–8 single spots in the area of leakage). In cases where energy was too low, as indicated by missing FA leakage, energy was adjusted and the patient re-treated immediately. Observation intervals were after 4 weeks and 3 months. In case of nonimprovement of the disease after 3 months, re-treatment was considered. ***Results:*** Of 10 patients with active CSC that presents focal leakage in FA, 5 had completely resolved fluid after 4 weeks and all 10 after 3 months. Mean visual acuity increased from 76.6 ETDRS letters to 85.0 ETDRS letters 3 months after SRT. Chronic-recurrent CSC was characterized by less severe SRF at baseline in OCT and weaker leakage in FA than in acute types. Visual acuity changed from baseline 71.6 to 72.8 ETDRS letters after 3 months. At this time, SRF was absent in 3 out of 16 patients (19%), FA leakage had come to a complete stop in 6 out of 16 patients (38%). In 6 of the remaining chronic CSC patients, repeated SRT with higher pulse energy was considered because of persistent leakage activity. After the re-treatment,

The study was and is registered at www.clinicaltrials.gov as NCT00403884 in Regensburg and currently as NCT02088151 in Bern.

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SRF resolved completely in 5 patients (83.3%) after only 25 days. ***Conclusion:*** SRT showed promising results in treating acute CSC, but was less effective in chronic cases. Interestingly, re-treatment resulted in enhanced fluid resolution and dry conditions after a considerably shorter time in most patients. Therefore, SRT including re-treatment if necessary might be a valuable CSC treatment alternative even in chronic-recurrent cases.

Introduction

Patients with central serous chorioretinopathy (CSC) complain of visual disturbances including metamorphopsia, central scotoma, reduced visual acuity and loss of contrast sensitivity [1]. CSC is usually characterized by idiopathic central leakage points with an exudative detachment of the neurosensory retina mostly in the macular area. Fluorescein angiography (FA) shows single or multifocal spots of fluorescein leakage at the level of the retinal pigment epithelium (RPE) [2, 3], indicating focal RPE defects. Indocyanine green angiography reveals choroidal hyperpermeability at the location of RPE leakage [4]. The main diagnostic and monitoring tool today is optical coherence tomography (OCT) that shows the amount of subretinal fluid (SRF) in acute cases. Resolution of modern OCT is sufficient to detect small RPE detachments within the region of neurosensory detachment [5, 6].

CSC has a favorable prognosis because SRF resolves in many cases within short time periods. In these cases, no treatment would be necessary. However, CSC can become chronic, and patients experience significant permanent visual impairment caused by recurrent episodes of acute CSC, persistent SRF and/or RPE atrophy [7]. Focal laser photocoagulation with continuous-wave lasers, such as argon (514 nm) or frequency doubled Nd-YAG (532 nm), is considered in cases without spontaneous fluid resorption. Such laser photocoagulation damages the neural retina: RPE cells, where the laser light is initially absorbed, are damaged directly by heating of the intracellular melanosomes, and the overlying photoreceptors are coagulated by heat diffusion. Subsequently, RPE bystander cells migrate and proliferate to cover the laser defect and ultimately re-establish an intact barrier [8–11].

Photocoagulation is not feasible in many cases of CSC since CSC usually affects the fovea and photoreceptor coagulation would lead to central laser scotoma. Selective destruction of RPE cells that improves metabolism and hydraulic conductivity at the chorioretinal junction while avoiding adverse effects to the neuroretina and to the photoreceptors may be a viable appropriate treatment option. Selective damage of RPE cells was first demonstrated by Roider et al. [12, 13] using 5-μs argon laser pulses at 514 nm with a repetition rate of 500 Hz. A train of short microsecond pulses generates high peak temperatures around the melanosomes leading to mechanical rupture of RPE cells, whereas sublethal temperature increase at the photoreceptors avoids their coagulation and laser scotoma [14].

Due to the lack of tissue coagulation, the selective lesions are ophthalmoscopically invisible and can only be visualized by FA, where they manifest as focal leakage in the early postoperative phase [14]. Selective destruction of RPE cells with sparing of photoreceptors was originally demonstrated by histological examinations in rabbits [12, 13, 15]. The first clinical trials, undertaken with a frequency-doubled Nd:YLF-laser (527 nm, 1.7-μs pulse duration, 100 pulses at 500 Hz and 30 pulses at 100 Hz), have proven the concept of selective RPE destruction and subsequent healing by RPE migration and proliferation; clinical improvement of different macular diseases was obtained, presumably due to enhanced metabolism at the chorioretinal junction and improved cellular RPE pump function [13, 16]. This treatment was named 'selective retina treatment' (SRT); an overview of the methods, techniques, preclinical and clinical results is given in Brinkmann et al. [17].

Thus, SRT seems to be an ideal treatment modality for CSC, especially if the RPE leak is located close to the fovea. Roider and coworkers [18] demonstrated a benefit of SRT in acute CSC by finding short SRF resolution times after treatment in a clinical case series and significantly better outcomes in the treatment group compared to a nontreatment group in a prospective randomized study [19]. However, due to the prototype character of this laser method, treatment numbers are still low and, additionally, we do not know whether chronic-recurrent CSC cases also benefit from SRT.

In this consecutive case series, we applied SRT in both acute and chronic-recurrent types of CSC to evaluate the clinical responses. To further reduce the necessary energy to induce RPE cell damage and, thus, reduce potential heat generation in the sensitive tissue of the fovea [14], we tested and compared the established 1.7-μs with 300-ns pulse durations.

We were aware of the fact that, during recent years, half-dose photodynamic treatment (PDT) was found to be effective in chronic cases. A meta-analysis by Ma et al.

[20] summarized results on 319 cases from 9 reports showing the best benefits for patients after PDT rather than after conventional focal laser or even anti-VEGF treatment. PDT therefore should be considered as the first-choice treatment in those cases. Therefore – derived from baseline angiographic findings – we tried mainly to focus on specific chronic-recurrent cases with 'clear' leakage areas. Such patients may eventually also profit from SRT in spite of being 'chronic' without the need for invasive and expensive PDT.

Material and Methods

Preliminary Remark

In this highly experimental study, the first prototype laser for SRT was used in a clinical setting. To date, no SRT laser is commercially available; thus, overall experience with SRT is very limited, and only 3 more machines have been built. By collecting clinical experience with our prototype, laser parameters and the laser delivery system have been adjusted and modified over years. Moreover, due to the fact that the first author moved twice during recent years, this paper reveals the 'collected' results from two sites over a time span of several years because of new installations, modifications and ethical approvals in Switzerland. However, a considerable number of patients have been treated with this feasible method; thus, for us it is worthy to share these promising results with the ophthalmologic society.

Patients and Examinations

Twenty-six patients with active acute (n = 10) or active chronic (n = 16) CSC were included in this two-center study. Twenty-one patients were treated at the University Eye Hospital in Regensburg, Germany, and 5 patients at the University Eye Hospital (Inselspital) in Bern, Switzerland. The study was approved by the local ethics committees and registered at www.clinicaltrials.gov as NCT00403884 (Regensburg site) and as NCT02088151 (Bern site).

Complete ophthalmologic examination, including ETDRS visual acuity, slit-lamp evaluation, indirect stereoscopic ophthalmoscopy after pupil dilation, FA and autofluorescence (Heidelberg Retina Angiograph HRA 2, Heidelberg Engineering GmbH, Germany) as well as SD-OCT imaging (Spectralis-OCT, Heidelberg Engineering) were undertaken before treatment and during the follow-up at 4 weeks and 3 months (and individually longer, if necessary, due to re-treatments) after SRT. Formation of choroidal neovascularization was ruled out in every case by FA and SD-OCT imaging. Further exclusion criteria for SRT were other retinal and macular diseases, prior macular and retinal treatments, such as laser, cryocoagulation or vitrectomy, as well as decompensated glaucoma.

Active CSC was identified by SRF in the foveal area as judged by SD-OCT before treatment. Acute CSC was defined by active focal leakage in FA and/or duration <3 months. Chronic-recurrent CSC was defined by a mottled appearance of RPE in FA with one or more spots of fluorescein leakage, which could be aimed at with laser, and/or a duration of SRF for more than 3 months. Irregular patterns of increased autofluorescence were also frequently observed in these patients [21]. If no clinical success was obtained within 3 months after initial treatment, SRT re-treatment was considered and individually followed up.

Laser and Settings

A clinical prototype SRT laser system (SRT vario; Medical Laser Center Lübeck GmbH, Lübeck, Germany), as described in more detail elsewhere [15], was used in this study. Briefly, the laser consists of a diode laser excited Q-switched Nd:YLF laser that generates a wavelength of 527 nm by intracavity frequency conversion. The duration of the Q-switched pulse can be adjusted from 200 ns to 3 μs by increasing the efficiency of the second harmonic generation into the overcoupling regime [22]. The laser was always operated at a repetition rate of 100 Hz and a train of 30 pulses was always delivered to each retinal spot. The maximal pulse energy of the laser system was 1 mJ. Five patients were treated with 1.7-μs pulse duration; this is the pulse duration originally used with SRT [23]. For most patients in this study, the pulse duration was reduced to about 300 ns since less laser energy is required for RPE cell disruption and, thus, less overall heat is produced [15, 23].

The laser light was coupled with an optical fiber either into an ophthalmic laser slit lamp (SL/L 30, Carl Zeiss Meditec AG, Jena, Germany) or into a scanning digital ophthalmoscope (SDO) (Wild GmbH, Völkermarkt, Austria). All Regensburg patients and the first Bern patient were treated with the slit lamp setup. The remaining 4 Bern patients received treatment with the SDO.

In both treatment devices, the emitted pulse energy was restricted to 400 μJ (1.7 μs) and 200 μJ (300 ns), respectively. A red diode laser beam (635 nm) served as the aiming light.

In the slit lamp setup, the fiber tip was imaged onto the fundus with an ophthalmoscopic contact lens (Mainster, OMRA-S), generating a retinal spot size of 200 μm. An ultrasonic transducer (Medical Laser Center Lübeck) was integrated in order to detect microbubble formation, which is the origin of selective RPE cell damage [24]. This optoacoustic device enabled the detection of the desired RPE cell damage for the ophthalmoscopically invisible SRT laser lesions in real time during treatment [12, 25]. Figure 1a shows the setting of the laser, the slit lamp and the optoacoustic device connected to the recording PC.

Since an SDO projects the laser beam onto the retina without the need of a contact lens, the feedback based on an ultrasonic transducer could not be used. Treatment monitoring instead was conducted using an external monitor and the live video derived from the SDO. Herein, aiming and treatment was guided by the live video image on the TV screen (fig. 1b).

Treatment and Dosimetry

Since human fundus pigmentation may vary among individuals and even within the fundus of 1 patient by a factor of two [26] or more, and the fact that the SRT lesions are ophthalmoscopically invisible, the cell damage energy needs to be adjusted for each patient. To this end, 5–10 test exposures were delivered at the lower vessel arcade and simultaneously recorded by optoacoustic measurements in each patient. The laser energy was increased until lesions became ophthalmoscopically visible, which occurs typically at twice the angiographic threshold, or until maximal laser energy was reached. FA was performed 1 h after this dosimetry measurement to determine the individual threshold energy for angiographic visibility. In FA for SRT dosimetry, focal leakage becomes visible in the test spots when the laser has damaged RPE

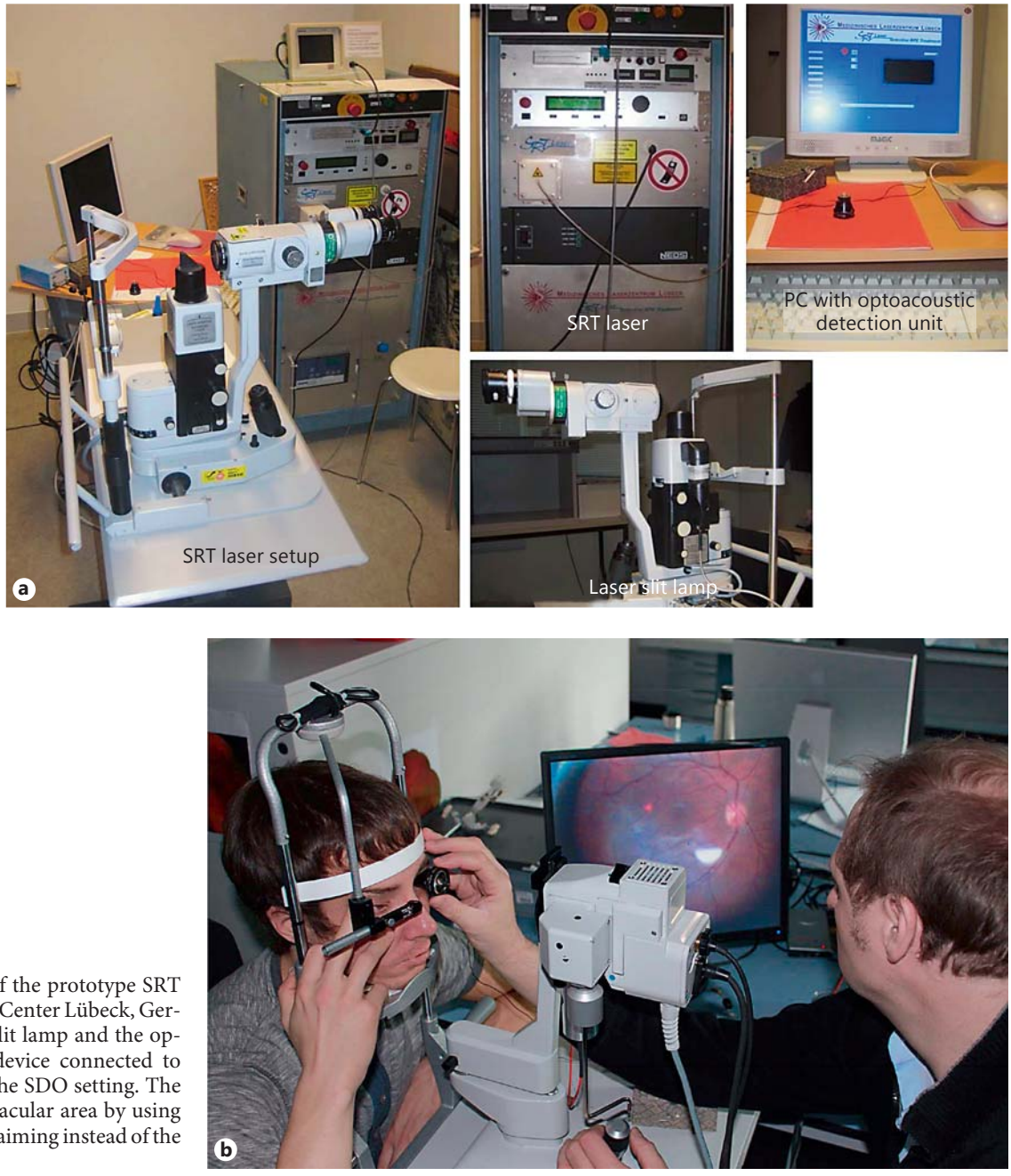

Fig. 1. a The setting of the prototype SRT laser built by the Laser Center Lübeck, Germany, with the laser slit lamp and the optoacoustic detection device connected to the recording PC. **b** The SDO setting. The physician treats the macular area by using the monitor image for aiming instead of the direct slit lamp setup.

cells and thereby compromised the integrity of the outer blood retinal barrier. Thus, absence of fluorescein leakage in the test spots indicates insufficient laser energy that is unable to damage RPE, i.e. the laser energy is below threshold. When the energy is too high, FA leakage along with increased light scattering in the test spot that resembles lesions generated by conventional laser photocoagulation most likely indicates adverse neuroretinal tissue damage (ophthalmoscopic threshold). The desired selective RPE damage is obtained when fluorescein leakage in the absence of ophthalmoscopic visibility is obtained (angiographic threshold).

The treatment energy was chosen slightly above the detected angiographic threshold but well below the ophthalmoscopic threshold to avoid the risk of central neuroretinal damage with an adequate safety margin.

Immediately after threshold determination, SRT energy was aimed at the CSC leakage points and/or the area of leakage. One hour after SRT, a second FA was performed to confirm that desired RPE damage was obtained. Re-treatment with SRT (re-SRT) was performed the same day with sufficient laser energy.

Table 1. Results of SRT in acute CSC, part 1

Case No.	Age, years	Type of leakage	Duration of single laser pulse, ns	Treatment energy, μJ	Laser spots, n	Lens status	SRF finally resolved?
2	39	pinpoint	1,700	200	5	clear	yes
5	47	pinpoint	1,700	200	5	clear	yes
6	37	pinpoint	300	100	6	clear	yes
10	44	pinpoint	300	160	5	clear	yes
13	50	pinpoint	300	120	5	clear	yes
B1	47	pinpoint	300	100	8	clear	yes
B2	44	pinpoint	300	120	7	clear	yes
B3	41	pinpoint	300	140	8	clear	yes
B4	56	pinpoint	300	120	20	clear	yes
B5	42	pinpoint	300	180	7	clear	yes

Table 2. Results of SRT in acute CSC, part 2

Case No.	VA			SRF			FA		
	baseline	4 weeks	3 months	baseline	4 weeks	3 months	baseline	4 weeks	3 months
2	90	80	95	1	0	0	1	0	0
5	75	80	95	1	0	0	1	0	0
6	75	75	75	1	1	0	1	1	0
10	70	80	75	1	1	0	1	1	0
13	80	75	95	1	0	0	1	0	0
B1	73	74	79	1	1	0	1	–	–
B2	84	79	84	1	1	0	1	–	–
B3	74	80	89	1	1	0	1	–	–
B4	72	78	79	1	0	0	1	–	–
B5	73	78	84	1	1	0	1	–	–

VA = Visual acuity (ETDRS letters); 1 = present; 0 = not present.

Results

Acute CSC

We treated 10 eyes of 10 patients with active acute CSC as characterized by pinpoint (PP) leakage and persistent SRF detected by OCT. The median age of the patients was 44 years (range 37–56 years). The mean baseline visual acuity was 76.6 ETDRS letters (range 72–90). All SRT treatments were performed without significant complications. Most importantly, no patient complained of central microscotoma after SRT. Five to eight treatment lesions were placed for treatment (median 6). The first 2 patients in Regensburg were treated with pulses of 1,700 ns, the other ones with pulses of 300 ns. Treatment energy with 1,700 ns was about 200 μJ. Energy was decreased by a factor of 1.5 when switching to 300-ns pulses (100–160 μJ). All SRT lesions were clinically invisible, with the exception of 1 patient. That patient was treated with 300 ns and pulse energy of 160 μJ in Bern. Small hemorrhage occurred at the laser site of two lesions but stopped spontaneously; thus, no further intervention was needed. Hemorrhages were resolved completely in the 3-month follow-up, and visual acuity increased from 73 to 79 ETDRS letters. FA visualized the SRT lesions in all patients about 1 h after SRT, confirming the desired cell damage effect. Thus, no immediate re-SRT was necessary.

SRF had completely resolved after SRT in 5 of the 10 patients after 4 weeks and in all 10 patients after 3 months. The mean visual acuity increased from 76.6 to 77.9 (4 weeks) and finally to 85.0 ETDRS letters at 3 months.

FA was performed at the Regensburg site at each follow-up visit (n = 5). No fluorescein leakage was observed

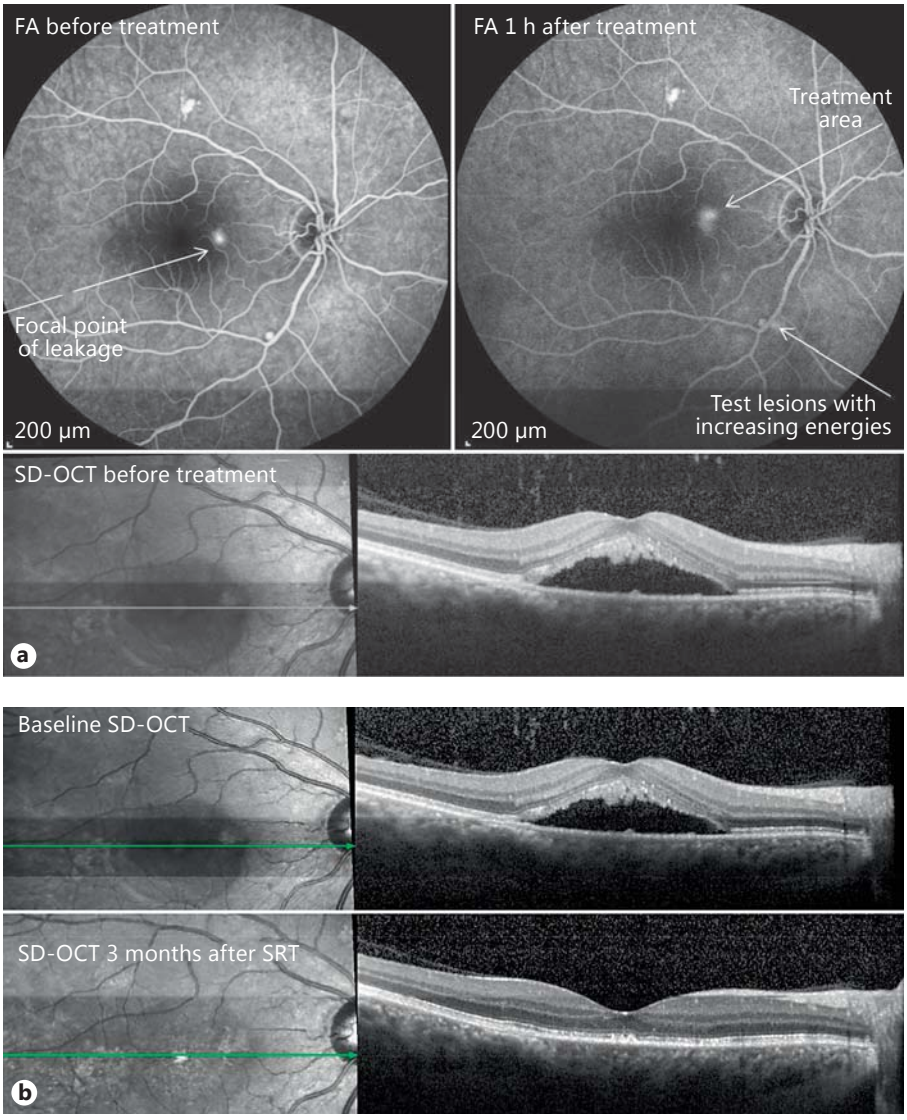

Fig. 2. Course of acute CSC treated with SRT. **a** FA before and after treatment and preoperative SD-OCT scan revealing SRF. **b** Three months after treatment, the SRF completely resolved. External limiting membrane is intact, indicating good visual acuity recovery.

in patients with resolved SRF. One of the 2 patients with persistent SRF after 4 weeks showed no SRF and no leakage after 3 months. In the second follow-up after 3 months, fluorescein leakage had ceased in all patients. All results for acute CSC are displayed in tables 1 and 2. A typical course of SRT in acute CSC is shown in figure 2.

Chronic CSC

Sixteen eyes of 16 patients with active chronic CSC were treated. All patients showed PP leakage and/or diffuse leakage in FA and persistent SRF judged by OCT. FA leakage was considerably less than in acute CSC, and subretinal precipitates were observed on a regular basis, indicating chronic disease. All 16 patients were male. The median age of the patients was 52 years (range 41–65 years). The baseline visual acuity was 71.6 ETDRS letters. All SRT treatments were performed without any complications. The median number of treatment lesions was 7 (range 3–14). The first 3 patients were treated with pulses of 1,700 ns, after reducing the pulse duration of the laser unit, the other 13 patients underwent SRT with pulses of 300 ns. The treatment energy of the first 3 patients was between 200 and 250 µJ; the treatment energy of the other 13 patients with 300 ns was 100–180 µJ. None of the SRT lesions was clinically visible. FA was performed to visualize the SRT lesions in nearly all of the patients 1 h after SRT. No patient complained of central microscotoma after SRT.

Table 3. Results of first SRT in chronic CSC, part 1

Case No.	Age, years	Type of leakage	Duration of single laser pulse, ns	Treatment energy, μJ	Laser spots, n	Lens status	SRF resolved?
1	46	2× old PP	1,700	250	4	clear	yes
3	55	2× old PP	1,700	200	9	clear	yes
4	40	PP + diffuse	1,700	200	4	clear	yes
7	49	PP + diffuse	300	120	3	clear	no
9	50	diffuse	300	140	4	clear	yes
12	41	diffuse	300	160	5	clear	no
16	54	PP + diffuse	300	140	4	inc.	no
19	47	diffuse	300	120–180	12	clear	yes
20	58	diffuse	300	120–160	12	clear	yes
21	51	PP + diffuse	300	120–140	14	inc.	no
8	54	2× PP	300	100	7	inc.	re-SRT
11	48	diffuse	300	120	6	clear	re-SRT
14	54	diffuse	300	120	7	inc.	re-SRT
15	48	PP + diffuse	300	140	6	clear	re-SRT
17	65	diffuse	300	140–160	8	clear	re-SRT
18	64	diffuse	300	200	8	cat.	re-SRT

Data are displayed for consecutive cases and cases in need of re-SRT. inc. = Incipient cataract formation; cat. = moderate cataract formation.

The follow-up after 4 weeks showed an absence of SRF in SD-OCT in 2 of 14 patients, while lack of fluorescein leakage on FA was observed in 5 of 14 patients (2 patients were missed at week 4). The mean visual acuity changed from baseline 71.6 to 72.8 ETDRS letters after 3 months (70.9 letters after 4 weeks). After 3 months, SRF had resolved in 3 out of 16 patients (19%), whereas a complete stop of leakage activity in FA was observed in 6 out of 16 patients (38%). Tables 3 and 4 give detailed information on the individual courses, on which some were recommended to receive PDT.

In 6 out of these 16 patients with chronic CSC, a second SRT with higher energy levels was performed because of persistent leakage activity in FA in addition to residual SRF. After re-treatment with SRT, the SRF was resolved in 5 of these 6 patients after a median time of 25 days (range 21–35 days). The mean visual acuity increased slightly from 71.7 to 72.5 ETDRS letters at 3 months (74.2 letters at 4 weeks). After 4 weeks, we observed no SRF in 4 of 6 patients and nearly resolved SRF in 1 patient; the reduction in SRF was accompanied by no leakage on FA in 4 of 6 patients. At the 3-month follow-up, we found resolved SRF in 5 and absence of leakage in 4 out of 6 patients. One patient with persistent SRF and leakage in FA was recommended for PDT. The results for re-SRT in chronic-recurrent CSC are displayed in tables 5 and 6. A typical course of re-SRT in chronic-recurrent CSC is shown in figure 3.

Discussion

CSC mainly affects young, working-age males and results in moderate-to-severe disturbances of vision. Although the disease frequently resolves spontaneously, the commonly used 'wait and see' approach may be questionable since these patients usually stay in their jobs and work on a daily basis. Because conventional laser photocoagulation leads to faster resolution but also results in central laser scars and blind spots [27, 28], waiting for self-improvement is justified. However, the novel laser treatment SRT selectively treats the RPE without harming the photoreceptors. It stabilizes the RPE layer and leads to enhanced pump function and fast resolution of the SRF [17–19] and, thus, offers a viable therapeutic approach for CSC. Selectivity of the SRT technique could be proven experimentally [12, 13] and clinically by microperimetric studies [25]. Moreover, a recent SD-OCT study in SRT laser lesions was also able to show the noncoagulating character of this laser technique in human eyes [29].

Until SRT becomes commercially available, one might consider medical treatment of CSC in acute and maybe also chronic cases. Since no 'gold standard' for the treatment of CSC is available yet, review articles and case series until 2012 suggest carbonic anhydrase, mild laser photocoagulation, SRT and PDT as well as intravitreal injections of bevacizumab, showing heterogeneous re-

Table 4. Results of first SRT in chronic CSC, part 2

Case No.	VA			SRF			FA			Remarks
	baseline	4 weeks	3 months	baseline	4 weeks	3 months	baseline	4 weeks	3 months	
1	95	95	95	1	1	1	1	1	0	A
3	70	65	65	1	–	0	1	–	0	
4	40	40	45	1	0	0	1	0	0	
7	60	60	60	1	1	1	1	1	1	B
9	70	70	70	1	1	1	1	1	1	C
12	75	75	80	1	1	1	1	0	0	D
16	75	75	75	1	1	1	1	1	1	E
19	75	75	90	1	1	0	1	0	0	
20	80	80	90	1	0	1	1	0	1	F
21	75	80	75	1	1	1	1	1	1	G
8	80	80	80	1	1	–	1	1	–	
11	70	75	75	1	1	1	1	1	1	
14	70	60	65	1	1	1	1	1	1	
15	75	70	65	1	1	1	1	1	1	
17	80	80	80	1	1	1	1	1	1	
18	55	55	55	1	–	1	1	–	1	

VA = Visual acuity (ETDRS letters); 1 = present; 2 = not present; A = after 6 months: no SRF and no leakage in FA; B = new leakage points, PDT recommended; C = new leakage point; D = decreased SRF, but no further control visit; E = PDT for chronic CSC, later bevacizumab for occult choroidal neovascularization; F = new leakage point after 3 months; G = new leakage points, PDT recommended.

Table 5. Results of re-SRT in chronic CSC, part 1

Case No.	Age, years	Months after first SRT	Type of leakage	Duration of single laser pulse, ns	Treatment energy, μJ	Laser spots, n	Lens status	Day at which SRF resolved
8	54	1	diffuse	300	120	4	clear	21
11	48	3	diffuse	300	140	6	clear	35
14	54	5	diffuse	300	140	7	inc.	no
15	48	3	PP + diffuse	300	180	8	clear	21
17	65	3	diffuse	300	160	7	inc.	27
18	64	4	diffuse	300	290	11	cat.	23

inc. = Incipient cataract formation; cat. = moderate cataract formation.

Table 6. Results of re-SRT in chronic CSC, part 2

Case No.	VA			SRF			FA			Re-marks
	baseline	4 weeks	3 months	baseline	4 weeks	3 months	baseline	4 weeks	3 months	
8	80	90	90	1	0	–	1	0	–	
11	70	80	80	1	0	–	1	0	–	
14	70	70	70	1	1	1	0	0	0	H
15	75	70	65	1	0	0	1	0	0	
17	80	75	70	1	0	0	1	0	0	
18	55	60	60	1	0	0	1	1	1	J

In cases 8 and 11, VA at 3 months was the last observation carried forward. VA = Visual acuity (ETDRS letters); 1 = present; 2 = not present; H = PDT recommended (persistent SRF, diffuse leakage point); J = SRT with maximal energy because of posterior subcapsular cataract, 5 months later cataract surgery in combination with intravitreal bevacizumab injection for occult choroidal neovascularization.

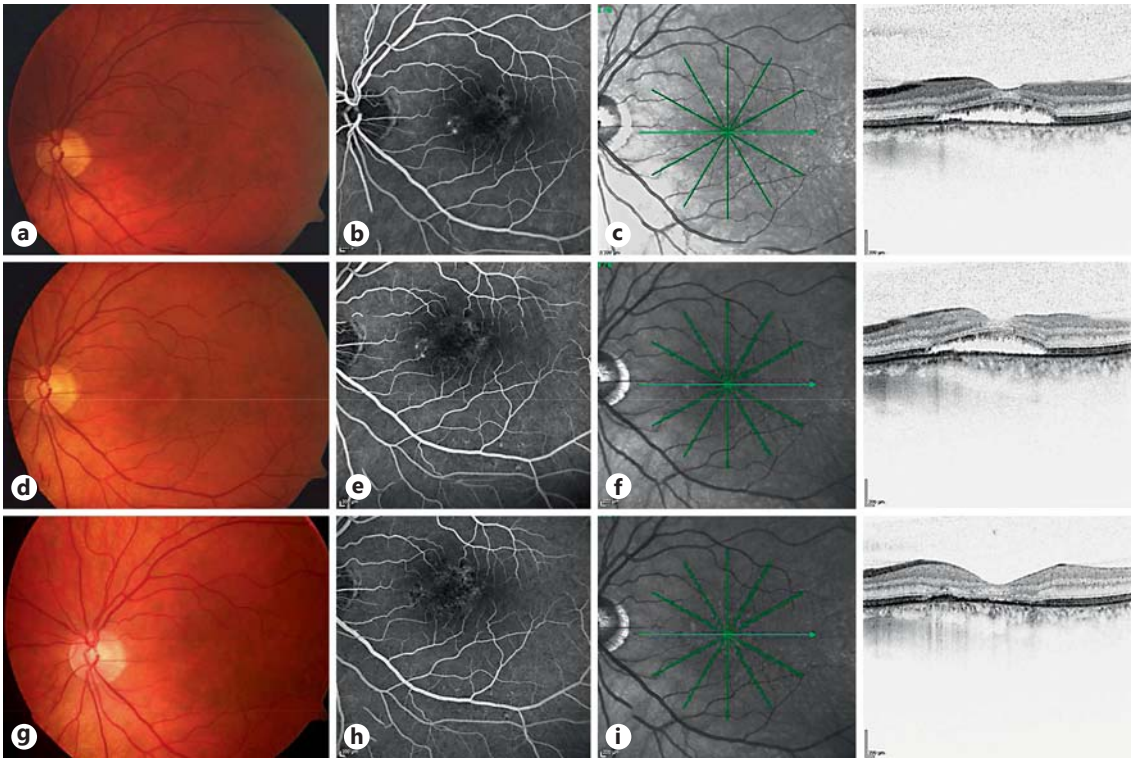

Fig. 3. Course of chronic-recurrent CSC treated with SRT and re-SRT. **a** At baseline, the fundus photograph revealed central pigment alterations indicating chronic CSC. **b** FA showed diffuse mottling and two PP leakages in the macular area. **c** In SD-OCT, SRF as well as subretinal precipitates were seen. **d** Three months after first SRT no clinical improvement was observed. No laser lesions around the PP leakages were seen on the fundus photograph. Test lesions at the lower arcade could be noticed by slight hyperfluorescent spots. Some central leakage was still seen (**e**), and SD-OCT revealed the same amount of SRF as before SRT (**f**). Four weeks after the second SRT using higher energy levels, laser lesions were still ophthalmoscopically invisible (**g**), but FA showed no leakage (**h**), and the corresponding SD-OCT revealed completely dry retinal conditions and even an intact external limiting membrane (**i**).

sults [30–32]. However, since it is known that glucocorticoids induce and aggravate CSC and are known to bind to the mineralocorticoid receptor, a blockade of these receptors might be of benefit in treating this disease with a specific mineralocorticoid receptor antagonist as spironolactone [33]. This beneficial effect could be demonstrated by a significant reduction of central macular thickness, SRF level, and an improvement in visual acuity [34]. However, the effect might be difficult to distinguish from the spontaneous course [35]. SRT might have the potential to overcome all described treatment options; however, this needs to be proven in direct comparative trials.

The clinical value of SRT in acute CSC has already been demonstrated in 2 different studies showing complete resolution of SRF in 85.2% of 27 patients within 4 weeks and a 100% resolution rate 3 months after irradiation [18]. The authors recommended early treatment in acute CSC using SRT [18] since neither visible coagulation nor complications occurred and the SRF resolved quickly after treatment. To confirm the benefit of SRT in active acute CSC, the same authors designed a prospective randomized trial and recruited 30 patients, from whom 14 eyes received SRT and 16 eyes served as control. Significantly better improvement of best corrected visual acuity (BCVA) of 12.7 ETDRS letters was observed in the laser group versus 6.3 letters in the control group and also SRF thickness decreased more significantly (203 vs. 41 μm) [19]. Eight eyes of the control group without BCVA increase within 3 months were then crossed over to the SRT group, and again significant BCVA increase (7.4 ETDRS letters) and SRF reduction (151.5 μm) were noticed after treatment [19].

Based on these results, SRT appears to be an interesting therapeutic option for the treatment of acute CSC. However, CSC presents very heterogeneously. While

many acute cases resolve spontaneously, CSC can manifest as a chronic or chronic-recurrent condition. Our main interest in this study was the evaluation of the first use of 300-ns laser pulses in CSC and the disease response of the chronic and chronic-recurrent forms of CSC to SRT.

Our results confirm a favorable course of acute CSC after SRT showing no SRF in all cases after 3 months. This is comparable with the results of Roider and coworkers [18]; however, our rate of complete SRF resolution was lower after 4 weeks (40%). One explanation might be the use of SD-OCT in our study in contrast to the OCT3 used in the cited study [18]. Modern SD-OCT affords higher axial resolution enabling the detection of very small residual SRF accumulations. Since even small residual SRF was judged as 'non-resolution' in our patients, a seemingly lower success rate may have been obtained if the older OCT 3 had missed residual SRF accumulations.

In chronic-recurrent CSC, diffuse hyperfluorescence with one or more PP lesions and progressive but weaker leakage is usually observed in FA. The RPE seems to be diffusely altered, which can be detected mainly by autofluorescence [21]. Since RPE barrier integrity in CSC seems to arise secondary to choroidal hyperpermeability [36], today photodynamic therapy (PDT) using full or half doses is often recommended on an 'off-label basis' in these cases [37, 38]. We test here if SRT can be a noninvasive and cheap alternative to PDT. SRT does not require the injection of a photoactive drug, and light exposure is confined to small irradiation spots that avoid the irradiation of the entire fundus. While an SRT therapeutic effect on the choriocapillary layer has not been demonstrated so far, but broad damage to it as with PDT is supposed to be avoided, the proof-of-principle for SRT therapeutic benefit in CSC is clearly given by Roider's group [18, 19].

We treated 16 patients with chronic-recurrent CSC to find out whether SRT might be helpful even in these cases. No adverse events were noted, and all laser lesions were ophthalmoscopically invisible. As expected, the BCVA and OCT results were worse than those of acute forms. No SRF resolution was observable in 10 out of 16 patients (62.5%) after 3 months. In those eyes with complete resolution, half of the eyes (n = 3) needed longer than 3 months (table 3).

Six patients with unsatisfying SRT outcomes were asked to undergo a second SRT treatment. While laser energy was adjusted above the initial levels, treatment within the therapeutic window between the angiographic and ophthalmoscopic threshold was always ensured. Interestingly, after re-SRT, SRF had disappeared completely within only 4 weeks in all but 1 patient (table 6). For the patient with no SRF resolution, PDT was recommended. Thus, SRT can also be effective in chronic-recurrent CSC, when treatment is repeated after potential initial treatment failure. Most likely, this effect is not due to increased pulse energy since the re-treatment still selectively targets RPE cells. More likely is the explanation that this method involves repeated stimulation at different time points; however, the exact mechanism is unknown.

Although the number of patients was small and the study not controlled, the long-lasting presence of SRF in these patients was impressively resolved within a very short time after re-SRT in spite of the previous treatment failure. While we conclude from this observation that the therapeutic response was in fact SRT derived, we also see the need to further investigate the efficacy and mechanism of this treatment. A prospective controlled study comparing PDT with SRT in chronic-recurrent CSC as determined, for example, by preoperative autofluorescence and chronic SRF in SD-OCT is worth considering. Such study could investigate the influence of parameters, such as the number of laser lesions, the density of the lesions, pulse energy as well as the number and best time points of re-treatments, on the efficiency of the treatment.

Since, especially in acute forms, treatment effects should be superior to the spontaneous course, which in principle has been already shown by Roider and co-workers [19], one might ask when an improvement can be expected following treatment. In all studies, earliest visits were performed 4 weeks postoperatively. However, since RPE regeneration regularly takes place within the 1st week after irradiation [8–10], clinical improvement might be expected within the 2nd week. In detail, this should be examined in a larger CSC trial. The best monitoring tool for such examinations is SD-OCT, whereas FA is supposed to be of less importance in clinical routine [39].

With respect to the two pulse durations used, we found that only 67% of the pulse energy is needed for 300 ns in comparison to 1.7 μs to obtain the desired RPE damage, as demonstrated by FA leakage. This outcome corresponds well with experimental findings on RPE cells [14] and with first clinical trials [15]. With respect to chronic CSC, it is notable, although not statistically significant, that SRF resolved in all the 3 patients treated with 1.7-μs pulses, while those patients with no improvement in SRF after 3 months were treated with 300 ns.

With respect to the different delivery setup in the study, i.e. once with a slit lamp and once with an SDO, no significant differences could be found despite the missing

stereoscopic visualization with the SDO. However, in some cases the operator noticed moderate video quality of the SDO. For the clinical outcome, no significant disadvantages have been observed.

A great benefit of the SRT technique is the virtual nonexistence of intraoperative complications afforded by the selective nature of the microsecond pulses that minimize heat diffusion into neurosensory tissue. In this study, complications occurred in only 1 patient, which is in accordance with the other SRT studies [18, 19]. Here, we noted the first exception when two small laser-induced hemorrhages appeared in the 1st patient in Bern. This occurred after the laser pulse duration was switched to 300 ns and much lower laser thresholds resulted. The patient did not notice any scotoma, and visual acuity improved during follow-up. The bleeding was most likely due to the slightly more explosive microvaporization at the different melanosomes from nanosecond pulses, which leads to larger coalescing bubbles than those resulting from the more timely deferred vaporization with microsecond pulses [40]. However, the basic reason for two small hemorrhages is unclear. Due to the fact that many patients were treated with pulse energies around 160 μJ and 300-ns pulse duration without any adverse effects, maybe a local hyperpigmentation in combination with an adjacent small vessel accounted for this effect.

Selective RPE damage can only be achieved with short microsecond pulses. Most of the other 'so-called' micropulse techniques are not able to confine the damage to the RPE and to completely avoid laser scotoma since they deliver pulses as, for example, 100 μs. RPE cells are damaged thermomechanically by the formation of microbubbles by nanosecond and short microsecond pulses, while thermal damage, that is, coagulation, is observed with pulses of a few milliseconds and longer. The transition of photodisruption to photothermal denaturation occurs at exposure durations between 20 and 50 μs [41, 42]. With SRT, axial and lateral heating of the tissue is confined to the absorbing RPE cells, whereas conventional photocoagulation is associated with strong heat diffusion into the neural retina and choroid with subsequent scotoma and scar formation. Therefore, selectivity with the sparing of photoreceptors is the most important benefit in laser-treated CSC because RPE leakage points are usually located near to the fovea, where classic laser coagulation should be avoided. Hence, SRT seems to be the appropriate laser technique.

In conclusion, SRT seems to be a valuable tool for early first-line treatment of acute CSC and maybe also in chronic-recurrent CSC. No adverse side effects are expected in a routinely used and commercially available laser system.

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