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Br J Ophthalmol published online June 15, 2010
doi: 10.1136/bjo.2009.178327

BJO Online First, published on June 15, 2010 as 10.1136/bjo.2009.178327

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C Klatt,[1] M Saeger,[1] T Oppermann,[1] E Pörksen,[1] F Treumer,[1] J Hillenkamp,[1] E Fritzer,[2] R Brinkmann,[3] R Birngruber,[3] J Roider[1]

[1]Department of Ophthalmology, University Medical Center Schleswig-Holstein, Kiel, Germany
[2]Institute for Medical Informatics and Statistics, Christian-Albrechts University of Kiel, Kiel, Germany
[3]Medical Laser Center Lübeck, Lübeck, Germany

Correspondence to
Dr Carsten Klatt, Department of Ophthalmology, University Medical Center Schleswig-Holstein, Arnold-Heller Strasse 3, Haus 25, Kiel D-24105, Germany; cklatt@auge.uni-kiel.de

Accepted 6 March 2010

ABSTRACT

Aims To evaluate selective retina therapy (SRT) as a treatment of acute central serous chorioretinopathy.

Methods 30 eyes of 30 patients with central serous chorioretinopathy of at least a 3 months' duration were recruited. 14 eyes were randomised to an SRT group (Q-switched neodymium-doped yttrium lithium fluoride (Nd:YLF) laser, wavelength 527 nm, t=1.7 μs, energy 100—370 μJ, spot diameter 200 μm, pulse repetition rate 100 Hz,) and 16 eyes to a control group. After 3 months of follow-up, patients in the control group with persistence of subretinal fluid (SRF) were allocated to a cross-over group, treated with SRT and followed up for further 3 months. The main outcome measures were change of best-corrected Early Treatment Diabetic Retinopathy Study visual acuity (BCVA) and SRF.

Results At 3 months of follow-up, the mean (SD) improvement of BCVA was significantly greater after SRT than in the control group: 12.7 (7.2) versus 6.3 (8.9) letters (p=0.04). SRF had decreased significantly more after SRT as compared with that the control group: 203 (136) μm versus 41 (150) μm (p=0.005). In eight eyes allocated to the cross-over group, the mean BCVA had increased during 3 months of follow up before SRT by 1.4 (5.2) letters and continued to increase during 3 months following SRT by 7.4 (6.3) letters, while SRF increased by 39.5 (160.2) μm before SRT and decreased by 151.5 (204.9) μm after SRT. In six of the eight eyes, SRF had completely resolved 3 months after SRT.

Conclusions SRT appears to expedite functional recovery and the re-absorption of SRF as compared with that in untreated controls. A larger prospective, randomised phase 3 confirmative patient study is warranted.

Trial registration number: NCT00987077

Acute central serous chorioretinopathy (CSC) characterised by serous detachment of the neurosensory retina often affects young men who experience visual disturbances including metamorphopsia, central scotoma, reduced visual acuity and loss of contrast sensivity.[1] Fluorescein angiography (FA) shows single or multifocal spots of dye leakage at the level of the retinal pigment epithelium (RPE). Indocyanine green angiography often reveals multifocal areas of choroidal vascular hyperpermeability.[2] Optical coherence tomography (OCT) shows various anatomical changes such as detachment of the neurosensory retina and/or of the pigment epithelium.[1]

Most episodes of CSC are self-limited and resolve spontaneously within 3—4 months.[3] Continuous wave (cw) laser photocoagulation expedites functional recovery in most cases,[4 5] but it is associated with side effects such as symptomatic scotoma and choroidal neovascularisation,[6] and in most patients, the long-term visual acuity is the same with or without cw laser photocoagulation.[7] Therefore, treatment is usually delayed by at least 3 months.[5] However, prolonged retinal detachment is associated with photoreceptor atrophy, and the duration of detachment appears to be negatively related to the functional outcome.[8] Although in most patients subretinal fluid (SRF) resolves and visual acuity recovers with or without cw laser photocoagulation,[7] some patients experience significant permanent visual impairment caused by recurrent episodes of CSC, persistent SRF and/or pigment epithelium detachment, and RPE atrophy.[9] Because most affected patients are young, persistent CSC episodes cause a significant loss of work hours. Furthermore, patients often complain of impaired colour and contrast sensitivity or metamorphopsia after prolonged detachment of the fovea. Consequently, retinal re-attachment within 4 months has been considered a relevant therapeutic target.[8] A treatment without side effects, which expedites functional recovery, could be applied early in the course of the disease. Selective retina therapy (SRT) selectively targets the RPE and spares the neurosensory retina[10–12] without causing microscotoma.[13–15] Therefore, SRT could be a therapeutic alternative to standard cw laser treatment, especially when leakage points are located close to the fovea.

This study was designed as a proof-of-concept phase 2 pilot study to evaluate SRT as a treatment of acute CSC. The main outcome measures were change of best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity (BCVA) and change of SRF as measured by OCT at 3 months of follow-up. The secondary outcome measures included the rate of complete absorption of SRF, presence of leakage in FA and systemic or ocular adverse effects.

PATIENTS AND METHODS

This study was a prospective, controlled, randomised clinical trial. A prototype Q-switched frequency doubled neodymium-doped yttrium lithium fluoride (Nd:YLF) laser suitable for SRT was available for the study period from April 2007 until June 2008. During this limited period, we recruited 30 eyes of 30 patients with acute symptomatic CSC and a documented disease progression of at least 3 months' duration.

The inclusion criteria were (1) minimum age of 18 years, (2) minimum history of 3 months of reduced visual acuity, (3) minimum BCVA of 20

ETDRS letters (20/200), (4) presence of SRF on OCT and (5) presence of active angiographic leakage in FA.

The exclusion criteria were (1) other retinal diseases, (2) glaucoma, (3) cataract or other media opacities, which preclude colour fundus photography (CFP) and FA, (4) previous photodynamic therapy or cw laser photocoagulation for CSC, and (5) systemic corticosteroid treatment, Cushing's disease, renal diseases, pregnancy and breastfeeding.

Informed consent was obtained from all participants. The study protocol was approved by the local ethics committee.

Sample size calculation

The sample size calculation was based on the detection of a large effect. A power of 80% applying the unpaired t test resulted in a sample size of 62 eyes. The level of significance for the two main outcome measures (BCVA and change of SRF) was corrected to 2.5% according to the Bonferroni correction.

Randomisation

Randomisation was performed by E.P. applying a balanced urn design procedure for a total number of 62 patients. Eyes were allocated to two groups at a ratio of 1:1—(1) treatment group and (2) control group. Sequentially numbered, opaque, sealed envelopes were prepared on the basis of the accomplished randomisation. The envelopes were administered by the blinded study nurse and opened at recruitment. A total of 14 eyes were randomised to the treatment group and received SRT at baseline. Sixteen patients were randomised to the control group who received no treatment within a follow-up time of 3 months. At 3 months' follow-up, patients in the control group with persistent leakage in FA and SRF in OCT were allocated to a cross-over group, treated with SRT, and followed for another 3 months.

Selective retina therapy

Treatment was performed with a Q-switched, frequency doubled Nd:YLF laser emitting at a wavelength of 527 nm (Medical Laser Center Lübeck GmbH, Lübeck, Germany). The pulse repetition rate was 100 Hz, and 30 pulses were released per exposure with a pulse duration of 1.7 µs. The fixed spot size diameter was 200 µm in air. A Mainster central field contact lens with a magnification of 1.05 was used. Laser spots were applied to focal points of leakage as assessed by FA.

Because the laser lesions are usually clinically invisible, optoacoustic (OA) measurements as described in detail elsewhere[10 16] were applied for dosimetry. Briefly, OA measurements detect the ophthalmoscopically invisible laser-induced damage of RPE cells and thereby overcome practical limitations of SRT.

Before each treatment, approximately five test shots with increasing energy were applied adjacent to the vessel arcades in order to determine the individually appropriate pulse energy for treatment by recording the OA value. The therapeutic OA value range is defined as 0.18—0.97. Within this range, 95% of treatment spots are visible by FA but funduscopically invisible.[16] FA was performed 1 h after treatment to visualise RPE damage by fluorescein angiographic leakage. Treatment spots visible in FA were achieved in all patients.

Baseline and follow-up examinations

Patients were assessed at baseline and followed up at 1 and 3 months. Patients in the control group without spontaneous resolution of SRF within 3 months' follow-up were treated with SRT and followed up for another 3 months.

At all visits, BCVA was assessed using ETDRS charts at 4 m distance. The investigator was blinded. Furthermore, slit lamp biomicroscopy, tonometry and funduscopy were performed at all visits. Ancillary tests consisted of CFP, FA, and OCT. OCT was performed with Stratus OCT 3 (Carl Zeiss Meditec, Jena, Germany) using the retinal map function centred on the fixation point. The maximum distance between the RPE and the outer neurosensory retina in the area of SRF accumulation was measured. FA was qualitatively assessed for the presence of leakage.

Statistical methods

In the statistical analysis of the outcome measures, a $p \leq 0.05$ was considered statistically significant. Comparisons of categorical variables between the two groups were performed using the two-tailed t test or the Fisher exact test, and continuous variables were compared using a two-tailed t test comparing the serial changes of parameters. The results were analysed using SPSS 15.0 software (SPSS Inc).

RESULTS

Thirty eyes of 30 patients with acute CSC were recruited. Fourteen eyes were randomised to the SRT group and 16 to the control group (figure 1).

In the limited time frame in which the laser was available, we enrolled 30 eyes of 30 patients. This is about half of the intended sample size of 62 patients. A retrospective power calculation based on the present data results in 55.7% power for detecting a statistically significant change of BCVA and an 83.5% power for detecting a statistically significant change of SRF at 5% level of significance.

All patients kept their follow-up appointment and were included in the analysis. Eight of 10 patients of the control group with persistent leakage in FA and SRF at 3 months' follow-up were treated with SRT and were followed up as cross-over group for another 3 months. Two patients declined further participation and were excluded from the study.

The mean (SD) age was 43.8 (5.6) years (range 35—54 years). Twenty-six (86.7%) patients were male. All baseline characteristics in terms of age, sex, proportions of patients with first and second or more CSC episodes, mean duration of current CSC episode, pattern of leakage point in FA and mean baseline BCVA were similar in both groups. Both groups differed slightly in the mean baseline SRF measured by OCT. The mean SRF at baseline in the SRT group was 387 (113) µm and in the control group, 320 (95) µm ($p=0.054$; two-tailed t test; table 1).

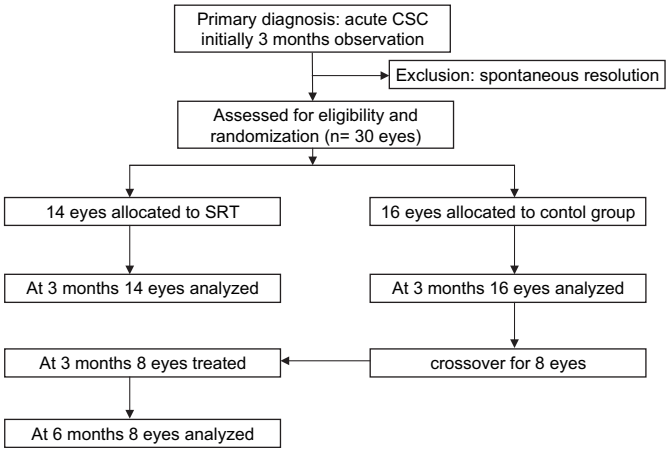

Figure 1 Flowchart showing the progression of patients in the study.

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The mean (SD) BCVA at baseline was 40.9 (9.9) letters (range 17–56 letters). The baseline FA in all 30 (100%) eyes showed fluorescein leakage at the macula consistent with idiopathic CSC.

The mean (SD) number of SRT laser spots in the SRT group was 9.3 (5.6) (range, 4–25). In the cross-over group, the mean (SD) number of SRT spots was 7.1 (2.7) (range, 4–13).

Overall, the mean (SD) treatment pulse energy used was 168.6 (31) μJ (range 120–270 μJ), and the recorded OA value was 0.24 (0.13) (range 0.03–0.51).

No adverse effects were noted during or after SRT, and no patients reported any adverse effects related to SRT or reported pain during laser application. None of the laser lesions were funduscopically visible either during treatment or 1 h following laser treatment or at subsequent follow-up visits. No signs of RPE change or atrophy were visible on funduscopy or CFP.

Change of BCVA

One month after treatment, the mean (SD) BCVA had improved in both groups. The mean BCVA in the SRT group improved from 40.1 (11.3) at baseline to 47.5 (7.9). The mean BCVA in the control group improved from 41.6 (8.9)–48 (8.7). At 3 months' follow-up, the mean (SD) BCVA in the SRT group had further improved to 52.8 (9.2), whereas BCVA in the control group remained at 47.9 (9.6) (p=0.043, two-tailed t test). The mean improvement of BCVA from baseline to 3 months' follow-up was 12.6 (7.2) letters in the SRT group and 6.3 (8.9) letters in the control group (figure 2).

Change of SRF

The mean (SD) baseline SRF in the SRT group and in the control group were 387 (113) μm and 320 (95) μm, respectively (p=0.054, two-tailed t test). At 1 month of follow-up, the mean (SD) SRF had decreased to 231 (86) μm in the SRT group and to 281 (81) μm in the control group. At 3 months' follow-up, the mean (SD) SRF remained significantly lower in the SRT group as compared with that in the control group: 184 (77) μm versus 287 (140) μm (p=0.005, two-tailed t test).

Ten (71.4%) of 14 patients in the SRT group had complete resolution of macular SRF at 3 months, compared with six (40%) of 16 eyes in the control group (p=0.081, the Fisher exact test). Overall, four patients in the SRT group had persistent SRF 3 months after the treatment. In two of these cases, FA showed occurrence of a new leakage point. In two other patients, persisting SRF was due to continuing leakage from the treated leaking point. In the control group, 10 patients (60%) had persistent SRF at 3 months' follow-up because of persistent leakage. Eight of these patients were allocated to the cross-over group and treated with SRT (figure 3).

FA and funduscopy

At 1 month of follow-up, 11 (78.6%) of 14 eyes in the SRT group showed a complete absence of fluorescein leakage compared with five (31.3%) of 16 eyes in the control group (p=0.014, Fisher's exact test).

At 3 months' follow-up, nine (64.3%) of 14 eyes in the SRT group showed a complete absence of fluorescein leakage compared with six (37.5%) of 16 eyes in the control group (p=0.272, Fisher's exact test). The increasing percentage of patients with fluorescein leakage in the SRT group at 3 months' follow-up was caused by the occurrence of new leakage points in three patients, two of whom had persistent SRF. In two other patients, continuing leakage was observed from the treated leakage point. An example of FA, CFP and OCT findings of a patient initially allocated to the control group and to the cross-over group at 3 months' follow-up is shown in figure 4. RPE atrophy, RPE rip or choroidal neovascularisation (CNV) was not found in FA or funduscopy.

Cross-over group

At 3 months' follow-up, 10 of 16 patients in the control group demonstrated persistent fluorescein leakage in FA, and OCT image showed persistence of SRF. Eight of these 10 patients agreed to SRT and were allocated to the cross-over group. SRT was performed immediately after the 3 months' follow-up visit. Further follow-up was performed 1 month and 3 months after SRT. The mean (SD) BCVA of these eight patients was 42.7 (5.1) letters at baseline. At 3 months' follow-up, the mean (SD) BCVA was 44.1 (5.4) letters. One month after SRT, the mean (SD) BCVA had improved to 48 (5.2). Three months after SRT, the mean (SD) BCVA had further improved to 51.5 (3.3) letters. The mean BCVA improvement in the cross-over group was 7.4 (6.0) letters since SRT and 8.8 (7.7) letters since baseline. The mean (SD) SRF in the cross-over group was 343 (75) μm at baseline

Table 1 Baseline demographics and clinical findings of 30 patients with acute idiopathic central serous chorioretinopathy (ICSC)

	All eyes (n=30)	SRT group (n=14)	Control group (n=16)	p Value
Mean (SD) age (yrs)	43.8 (5.6)	42.8 (5.5)	44.7 (5.7)	0.360*
Sex				
Male	26 (86.7%)	14 (100%)	12 (75%)	
Female	4 (13.3%)	0	4 (25%)	0.103†
Number of ICSC episodes				
First	16 (53.3%)	7 (50%)	9 (56.3%)	
Second or more	14 (46.7%)	7 (50%)	7 (43.7%)	>0.990†
Characteristics of leakage points in fluorescein angiography				
One focal leakage point	17 (56.7%)	8 (57.1%)	9 (56.3%)	
Two focal leakage points	1 (3.3%)	0	1 (6.2%)	
Diffuse leakage	12 (40%)	6 (42.9%)	6 (37.5%)	>0.990†
Presence of pigment epithelium detachment in OCT	3 (10%)	1 (7.1%)	2 (12.5%)	>0.990†
Mean (SD) duration of current ICSC episode (months)	9.0 (6.6)	9.4 (6.8)	8.6 (6.6)	0.746*
Mean (SD) baseline BCVA (ETDRS letters)	40.9 (9.9)	40.1 (11.3)	41.6 (8.9)	0.691*
Mean (SD) baseline maximum SRF (μm)	351.2 (95.4)	386.8 (112.6)	320.1 (66.3)	0.054*

ICSC, idiopathic central serous chorioretinopathy; logMAR BCVA, logarithm of minimal angle of resolution best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; SRF; subretinal fluid.
*Two-tailed t test.
†Fisher exact test.

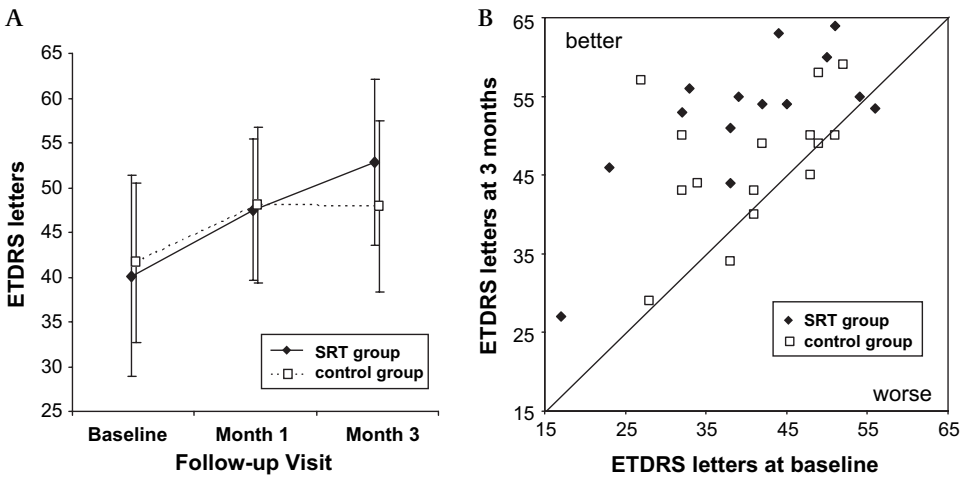

Figure 2 (A) Change of best-corrected visual acuity (BCVA) in ETDRS letter score of patients in the SRT group and in the control group. Error bars represent SD. (B) Scatter plot of BCVA of patients in the SRT group and in the control group at baseline and at 3 months' visit. The difference of BCVA between baseline and 3 months' visit was statistically significant (p=0.043, two-tailed t test).

and increased to 374 (135) µm at 3 months' follow-up. One month after SRT, the mean (SD) SRF had decreased to 245 (102) µm, and 3 months after SRT, the mean (SD) SRF had further decreased to 222 (131) µm. In six (75%) of eight patients, SRF had completely resolved 3 months after SRT.

DISCUSSION

The results of the present study show that SRT appears to expedite functional recovery and the re-absorption of SRF as compared with untreated controls. At 3 months' follow-up, the mean improvement of BCVA and re-absorption of SRF were significantly greater after SRT than in the control group. There was a tendency, although statistically not significant, towards a greater number of patients with complete resolution of SRF at 3 months after SRT as compared with controls (71.4% and 40%, respectively). The outcome of the cross-over group also demonstrated the efficacy of SRT in CSC cases with a well-documented history of persistent leakage in FA, persistence of SRF and unchanged BCVA for 6 months. No adverse effects were noted during or after SRT, and no patients reported any adverse effects related to SRT.

Established treatment methods for CSC include cw laser photocoagulation[4 5 7 17], photodynamic therapy[18 19] and treatment with a micropulse diode laser (MDL).[6] Because of the described side effects of cw laser photocoagulation, the common current approach is to treat with a cw laser only when SRF has not spontaneously resolved within an extended period of observation. In compliance with the current clinical practice of laser treatment for CSC, we only enrolled patients with a minimum history of 3 months' persistence of SRF. Considering the threat of atrophic changes of the photoreceptor layer caused by persistent SRF, we also treated patients in the control group with SRT when SRF persisted for 6 months (3 months before and 3 months after enrolment). Our study design aimed to prevent atrophic photoreceptor changes caused by persistent SRF, while this study design precludes the comparison with the functional long-term outcome with observation only.

A similar approach of RPE selectivity is claimed by MDL.[6] Chen *et al* reported effective treatment of acute CSC with an 810 nm MDL (Iris Medical Oculight Slx Laser; Iridex, Mountain View, California, USA), which operates with laser trains consisting of 300 µs micropulses delivered over a period of 2 ms (300 µs on and 1700 µs off). However, optimal laser parameters for the treatment of CSC with MDL are under development, problems concerning dosimetry are yet unsolved and micro-perimetry excluding MDL-treatment related scotoma has not yet been reported.[6] Inspite of similarities of MDL and SRT, the respective effect on RPE cells is different. With a pulse duration of <50 µs as used in SRT, the damage mechanism changes from solely thermal to a thermomechanical disruptive effect[20] caused by microbubbles, which form in exposed cells when the vapourisation threshold temperature at the melanosomes is exceeded. While microbubble-related damage is cell selective, thermal effects are not. In principle, to truly selectively target the RPE, microsecond pulse durations are better suited than diode laser systems with several hundred microsecond pulses. An

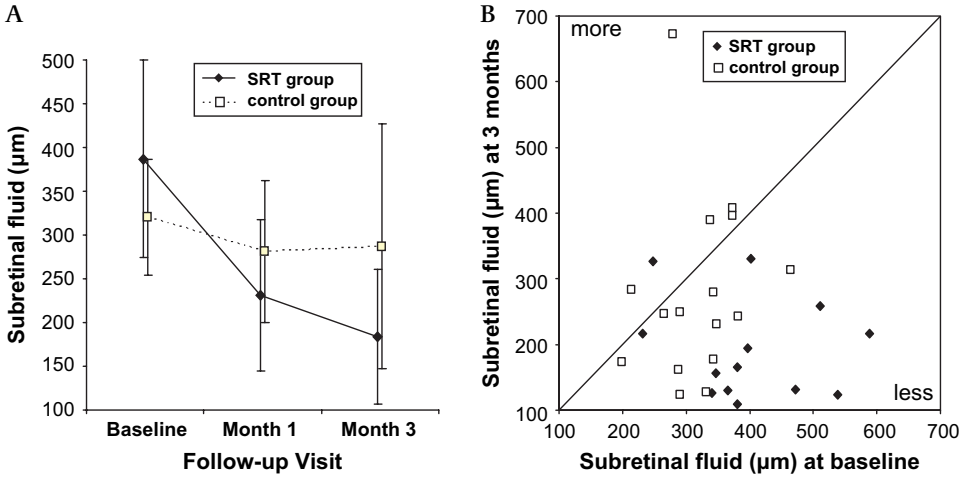

Figure 3 (A) Change of subretinal fluid (SRF, maximum distance between the RPE and the outer neurosensory retina in the area of SRF accumulation) measured by OCT in the SRT group and in the control group. Error bars represent SD. (B) Scatter plot of SRF of patients in the SRT group and in the control group at baseline and at 3 months' visit. The difference of BCVA between baseline and 3 months' visit was statistically significant (p=0.005, two-tailed t test).

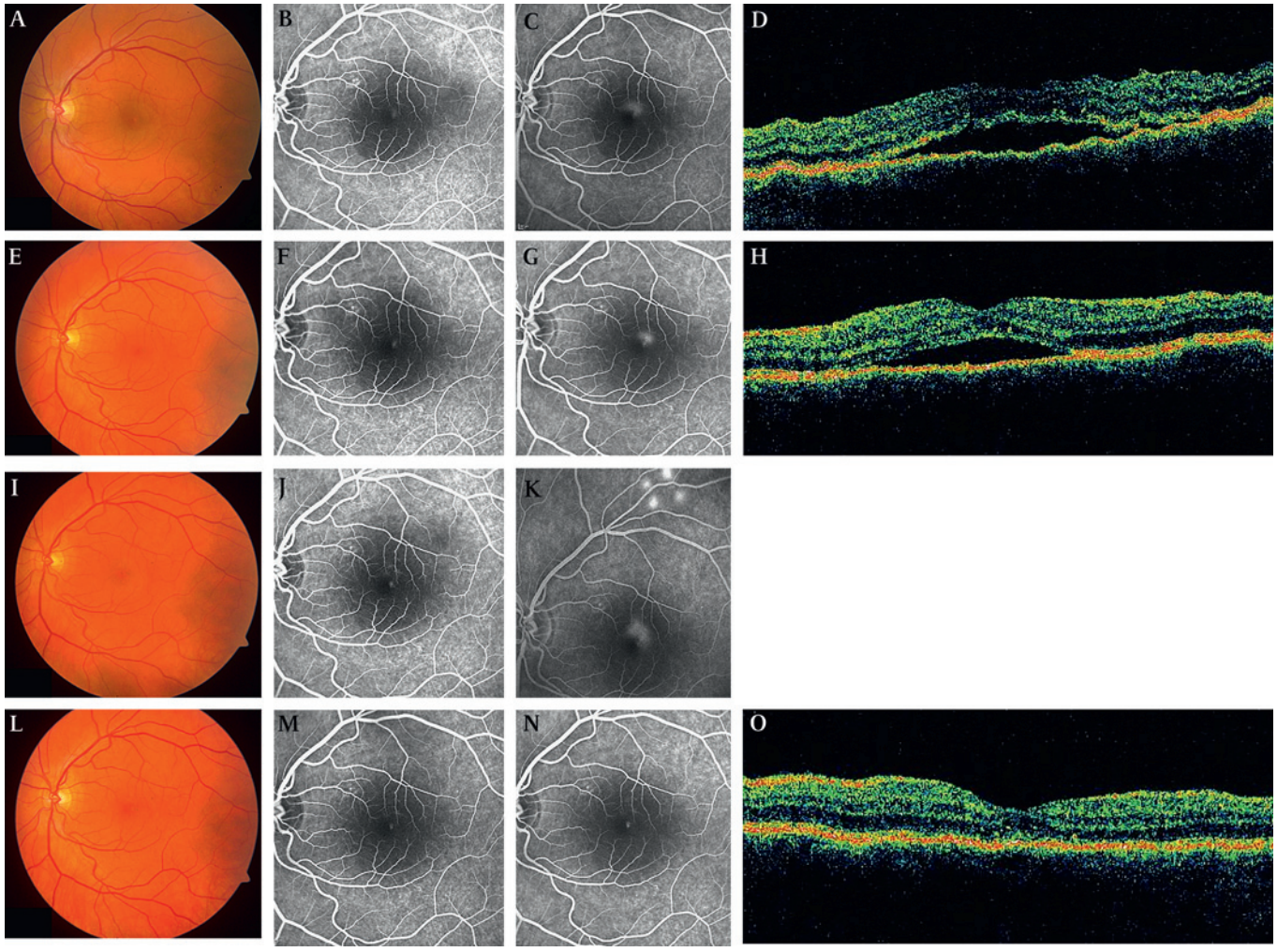

Figure 4 Left eye of a 40-year-old man with central serous chorioretinopathy (CSC) since 10 months who was randomised into the control group and received SRT after a follow-up of 3 months. The baseline Early Treatment Diabetic Retinopathy Study (ETDRS) letter score was 32 letters. (A) Colour fundus photography (CFP). (B) Early-phase and (C) late-phase FA at baseline showed pin-point leakage with fluorescein leakage close to the fovea. (D) Baseline optical coherence tomography (OCT) image showing subretinal fluid (SRF) involving the fovea. At 3 months without any therapy so far, the ETDRS letter score improved to 43 letters. (E) CFP after 3 months' follow-up. (F) Early-phase and (G) late-phase FA images demonstrating persistence of fluorescein leakage close to the fovea and (H) OCT image obtained at 3 months showing persistent SRF. (I) CFP 2 h after SRT showing no whitening in the area of test and treatment spots in terms of retinal burning. However, SRT spots can be detected by increasing leakage with early-phase (J) and late-phase (K) FA accomplished 1 h after SRT. At 3 months after SRT, the ETDRS letter score improved to 53 letters. (L) CFP showing no laser scars, (M) early-phase and (N) late-phase FA images demonstrating absence of fluorescein leakage at the macula. (O) OCT image obtained at 3 months after SRT showing complete resolution of the SRF.

ideal laser medium to generate microsecond pulse durations is neodymium-doped yttrium lithium fluoride (Nd:YLF) operated in the Q-switched, intracavity frequency-doubled regimen (wavelength 527 nm).[21] Furthermore, limitations of the practical use of SRT have recently been overcome by opto-acoustic measurements, which provide non-invasive, real-time dosimetry during the application of treatment.[10 16]

One limitation of the presented pilot study is the small number of patients. On the basis of the promising findings of this investigation, a larger prospective, randomised, controlled confirmative phase 3 study including functional tests like microperimetry and retinal autofluorescence monitoring RPE changes is needed to further test the efficacy and the safety of SRT as a treatment of acute CSC. Possibly, SRT could be applied at an earlier stage of the disease to prevent detachment of the fovea for patients who need rapid recovery, if there is evidence of micro-architectural changes in the macular retina, if visual acuity declines to 20/40 or less or in case of a history of multiple recurrences.

Competing interests Declared. Johann Roider, Ralf Brinkmann and Reginald Birngruber hold patents on selective retina therapy. Carsten Klatt, Mark Saeger, Till Oppermann, Erk Pörksen, Felix Treumer, Jost Hillenkamp and Elfriede Fritzer have no competing interests.

Ethics approval This study was conducted with the approval of the University Medical Center of the Christian-Albrechts-University, Kiel.

Provenance and peer review Not commissioned; externally peer reviewed.

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