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RETINAL DISORDERS

# Selective retina therapy (SRT) for clinically significant diabetic macular edema

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**Abstract**
*Purpose* To test selective retina therapy (SRT) as a treatment of clinically significant diabetic macular edema (DME).
*Methods* Prospective two-center interventional uncontrolled phase II pilot study. Thirty-nine eyes of 39 patients with previously untreated non-ischemic DME were treated with focal laser treatment using a Q-switched frequency doubled Nd:YLF laser which selectively affects the retinal pigment epithelium while sparing the photoreceptor layer. Optoacoustic measurements, fundus fluorescein angiography (FFA), and funduscopy were used to determine the individual threshold of RPE damage of each patient. The pulse energy was adjusted to apply angiographically visible but funduscopically invisible effects. Optoacoustic measurements were correlated with funduscopy and FFA. Follow-up examinations at 3 and 6 months post-treatment included best-corrected ETDRS visual acuity (BCVA), FFA, fundus photography, and retinal thickness measured by optical coherence tomography. The primary outcome measure was change of BCVA. Other outcome measures were change of retinal thickness, presence of hard exudates, leakage in FFA, accuracy of optoacoustic measurements, and correlation of BCVA with change of anatomical and systemic parameters.
*Results* Mean BCVA improved from 43.7 letters (standard deviation, SD=9.1) at baseline to 46.1 letters (SD=10.5) at the 6-month follow-up ($p$=0.02). BCVA improved (>5 letters) or remained stable (±5 letters) in 84% of eyes. Thirteen percent of eyes improved by ≥10 letters, while 16% of eyes lost more than 5 letters. There was no severe loss of vision (≥15 letters). Overall, retinal thickness, hard exudates, and leakage in FFA did not change significantly ($p$>0.05), while improvement of BCVA correlated with a reduction of hard exudates ($p$=0.01) and central retinal thickness ($p$=0.01). Specificity and sensitivity of detecting the angiographic visible threshold of RPE damage by optoacoustic measurements were 86% and 70% respectively. No adverse effects or pain were noted during or after treatment.
*Conclusions* Functional and anatomical improvement or stabilization was observed in most patients. SRT appears to be safe. Optoacoustic measurements accurately detect the individual threshold of RPE damage. A randomized trial is required to further test efficacy and safety of SRT as a treatment of clinically significant diabetic macular edema (DME).

**Keywords** Diabetic macular edema · Diabetes · Laser · Selective retina therapy · SRT

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## Introduction

Diabetic retinopathy is the leading cause of reduced vision and blindness in diabetic patients [1–4]. In 2004, the World Health Organization identified diabetic retinopathy as the 5th most common cause of blindness worldwide [5]. Laser photocoagulation has been well-established by large multicenter, prospective studies as a beneficial treatment of diabetic macular edema (DME) [6]. The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that argon laser photocoagulation reduces the risk of severe visual loss by 50% or more in patients with clinically significant DME [6]. Despite the introduction of intravitreal anti vascular endothelial growth factor (VEGF) therapy and triamcinolone as a treatment of DME, laser photocoagulation continues to be the gold standard of treatment [7]. At present, the standard laser treatment is applied using a continuous wave green wavelength laser (514 nm or 532 nm). Laser energy is increased until funduscopically visible white or grey laser lesion become visible. Heat is conducted to the adjacent tissues causing irreversible thermal damage to photoreceptors and choroidal tissue [8, 9]. Thus, laser treatment of the macula can cause direct scotomas at the treatment sites as well as indirect scotomas due to progressive enlargement of laser scars [10, 11].

In DME, extracellular fluid accumulates within the retina due to impairment of the inner and outer blood retinal barriers. Scars in the retinal pigment epithelium (RPE) layer reduce the overall capacity of the RPE to actively transport water from the retina to the choroid; hence, repeated standard laser treatments of the macula may increase the accumulation of intraretinal fluid [2, 12]. Although laser treatment has been shown to be effective in DME [2, 6], the exact underlying mechanism of the therapeutic effect is not fully understood. Several mechanisms have been suggested, including the modulation of chemical factors, thermal vascular thrombosis or sclerosis and alterations in the blood–retinal barriers [13–15]. It has been shown histologically that RPE can regenerate following either conventional laser treatment or selective retina therapy (SRT), re-establishing a normal RPE monolayer [16]. One theory postulates that the beneficial effect of photocoagulation is associated with the establishment of a new barrier of RPE cells, with a subsequent restauration of the RPE pump and the integrity of the RPE as a barrier [13]. Based on this theory, the destruction of tissue adjacent to the RPE, in particular the photoreceptors, is an unwanted side-effect. These theoretical considerations have lead to the development of the SRT laser treatment that affects selectively the RPE as previously described [9, 17]. Briefly, thermal modelling as well as in vitro and in vivo studies have shown that the spatial extent of elevated temperatures is reduced when multiple laser pulses with a short duration and a low repetition rate are applied. With these parameters, the effect of the laser exposures remains localized to the main light-absorbing structures such as the intracellular melanosomes of the RPE, while the photoreceptor layer, Bruch's membrane and the choroid are spared [9, 16, 18]. Schüle et al. have shown that laser effects in the RPE just above the damage threshold are thermal in nature for pulse durations >50 μs, but thermomechanically disruptive due to microbubble formation following vaporisation around the intracellular melanosomes for pulse durations of less than 10 μs [19]. The threshold irradiance for RPE damage in the thermomechanical regimen decreases almost linearly with shorter pulse duration [18] and the vaporisation becomes stronger and more explosive towards nanosecond pulse durations [20]. In order to reduce thermal damage and avoid strong disruptive effects, the microsecond-pulse duration regimen is so far regarded as optimal for selective effects targeting the RPE [17].

The formation of microbubbles generates a pressure wave which travels through the eye. This pressure wave can be detected at the cornea with an ultrasonic transducer embedded in a contact lens. We have shown that the appearance of microbubbles correlates with RPE damage as detected by fundus fluorescein angiography (FFA), and thus the appearance of microbubbles can be used as an appropriate indicator of RPE damage [18]. Based on the discussed concepts and results, a medical laser system was developed (Medical Laser Center Lübeck GmbH, Lübeck, Germany) operating at a wavelength of 527 nm and a pulse duration of 1.7 μs. This pulse duration was shown experimentally to be safe for smooth cell disruption by microbubbles, and thus gentle RPE treatment (SRT) [18, 19]. Because of the invisibility of the gentle effects close above damage threshold, the detection of RPE effects with an optoacoustic device and a suitable evaluation algorithm was tested in the present study as a realtime feedback dosimetry tool, and correlated with FFA and funduscopy.

The aim of this study was to test the effect of selective retina therapy (SRT) as a treatment of clinically significant DME.

The primary outcome measure of the study was change of best-corrected ETDRS visual acuity (BCVA). Other outcome measures were (1) change of retinal thickness, (2) presence of hard exudates and leakage in FFA, (3) specificity and sensitivity of optoacoustic measurements in detecting the individual angiographic visible threshold of RPE effects, and (4) correlation of BCVA with change of anatomical (retinal thickness, presence of hard exudates, and leakage in FFA) and systemic parameters [haemoglobin (Hb) $A_{1C}$, serum glucose, serum creatinine, blood pressure].

## Patients and methods

This was a prospective two-center interventional uncontrolled phase II pilot study. The study is registered with http://www.clinicaltrials.gov, no.: NCT00994955. Ethics committee approval was obtained. Informed consent was obtained from all patients. Forty eyes of 40 patients with clinically significant DME [6] were recruited from the Medical Retina services of the University Eye Hospitals in Kiel and Lübeck, Germany. A detailed medical history including the ocular history was obtained. Prior to treatment, and 3 and 6 months after treatment, BCVA with ETDRS charts at 4 meters distance was assessed. Following dilation of the pupil all patients underwent slit-lamp biomicroscopy, indirect funduscopy using a 78 diopter lens, color fundus photography (CFP), FFA or indocyanine green angiography (ICGA) (HRA, Heidelberg Engineering, Heidelberg, Germany), and optical coherence tomography (OCT) (OCT 3, Zeiss Meditec, Jena, Germany). A standardized OCT scan consisted of six radial scans (6 mm length), at 30-degree intervals, each with an axial length of 2 mm, centered on the patients' fixation point.

### Inclusion criteria

Minimum age of 18 years and the presence of clinically significant DME according to the criteria of the ETDRS study [6].

### Exclusion criteria

Ischemic DME defined as foveal avascular zone disrupted by capillary closure in more than 30% of the central circle on FFA, rubeosis iridis, significant media opacity compromising FFA and CFP, previous intraocular surgery, previous macular laser treatment, other retinal vascular disease, glaucoma, and known allergic hypersensitivity to fluorescein, indocyanine green, or iodine. General exclusion criteria included pregnancy or breast-feeding and significant medical conditions such as renal failure.

### Selective retina therapy (SRT)

All patients were treated with the SRT-Laser system (Medical Laser Center Lübeck GmbH, Lübeck, Germany), a Q-switched frequency doubled Nd:YLF laser (527 nm), operating with a pulse repetition rate of 100 Hz. The pulse duration (full width at half maximum) is 1.7 µs. The laser energy is transmitted via fiber to a Lumenis slit lamp allowing the application of a fixed spot size with a top head diameter of 200 µm in air. Per foot switch, 30 pulses are released; the pulse energy can be chosen by the physician up to a maximum of 400 µJ (Table 1). A Mainster central field contact lens with a magnification of 1.05 was used for all irradiations. Laser spots were applied to areas of focal leakage. As previously described, prior to each treatment 10–20 test shots were applied adjacent to the vessel arcades, in each patient (Fig. 1), in order to determine the individually appropriate pulse energy for treatment. One to 2 hours later, FFA was performed to evaluate the test spots. The minimum pulse energy that resulted in visible leakage at the test sites, as demonstrated by hyperfluorescence on FFA without causing a clinically visible laser lesion, was selected as the treatment energy for that individual patient [21]. Pulse energies that resulted in a clinically visible white/grey laser lesion detected a few seconds after application were considered 'over-treatment' for that individual, most likely indicating photoreceptor damage. ICGA was performed in selected patients when FFA was not sufficient for analysis of test spots due to pronounced

**Table 1** SRT irradiation parameters

| | |
|---|---|
| Wavelength | 527 nm |
| Single pulse duration | 1.7 µs |
| Maximal single pulse energy | 400 µJ |
| Number of pulses per laser spot | 30 |
| Pulse repetition rate | 100 Hz |
| Overall time per exposure | 300 ms |
| Spot size at retina | 210 µm |

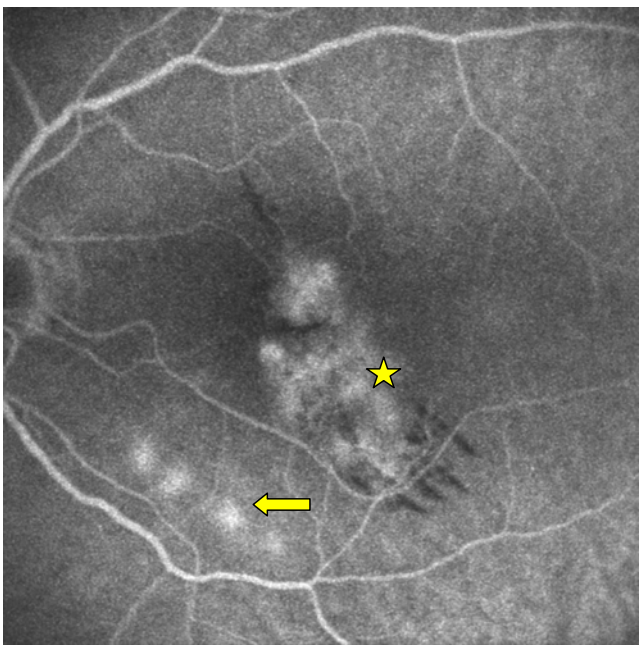

**Fig. 1** Laser test spots applied using different single pulse energies. Analysis of the test spots (*yellow arrow*) of the angiograms were used to choose the proper energy for treatment of the central pathology (*yellow star*)

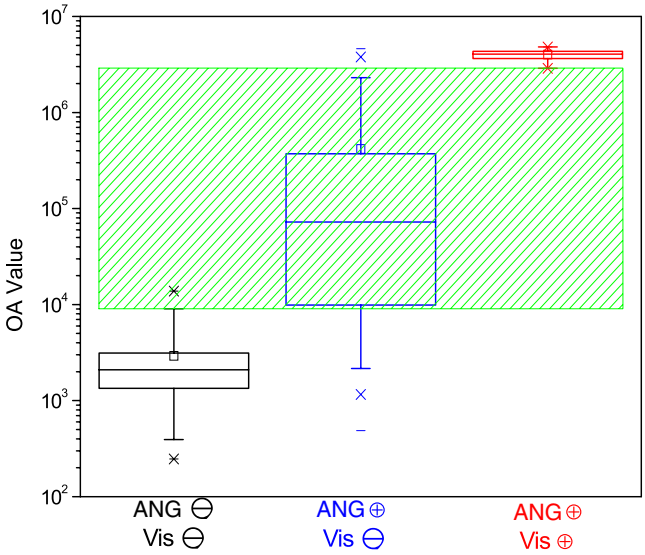


**Fig. 2** Box–whisker plot of measured OA values for ANG (−) / Vis (−), ANG (+) / Vis (−) and ANG (+) / Vis (+). The box is determined by the 25th and 75th percentiles while the whiskers determine the 5th and 95th percentiles. Additionally the maximum, minimum, the mean and the 99th as well as 1st percentiles are included. The green shaded area depicts the treatment range between the 95th percentiles of the maximum of ANG (-) / Vis (-) ("under-treatment") and the minimum of ANG (+) / Vis (+) ("over-treatment")

background leakage from diabetic fundus changes. SRT re-treatment was carried out at 3 months or 6 months in cases of worsening of DME based on the FFA leakage pattern, and macular thickening as measured by OCT.

## Optoacoustic dosimetry

Since the laser spots are usually clinically not visible, optoacoustic measurements were included in the study. The purpose was to test the optoacoustic measurement procedure as an online control procedure during laser treatment to verify therapeutic effects without subsequent FFA. The formation of microbubbles around the strong absorbing melanosomes inside the RPE has been identified as the leading mechanism of RPE damage during microsecond laser pulse exposure [18]. When energy is absorbed and converted to heat, the thermoelastic expansion of the absorbing medium as a matter of principle leads to the emission of a bipolar pressure wave. After exceeding the vaporization threshold, additional transients will be emitted owing to the formation and collapse of multiple microbubbles. Due to the microsecond heating and cooling and to the microsecond bubble lifetime, both thermo-elastic and bubble-induced pressure waves are in the ultrasonic MHz frequency range. The microbubble-related pressure waves appear as statistical fluctuations overlaying the thermoelastic waves. A mathematical algorithm was therefore derived to separate these fluctuations from the thermo-elastic background, as described in detail by Schüle et al. [22]. The algorithm gives a number which is related to the maximal pressure differences between thermo-elastic and bubble waves, the so-called OA value [22]. In order to non-invasively detect the acoustic transients during patient treatment, a contact lens was modified with an ultrasonic transducer. Thereby, the pressure waves were recorded, evaluated by computer and displayed on a monitor directly after each laser spot was applied. Optoacoustic (OA) values of the test lesions were later correlated to the threshold of RPE damage as detected by FFA or ICGA (ANG) (Figs. 1 and 2). This OA dosimetry procedure was performed as part of the SRT study protocol, and was analyzed by relating the OA values to the angiographic leakage activity and the funduscopic visibility in a subgroup of 19 patients (232 lesions).

## Follow-up

Follow-up was 3 and 6 months after laser treatment. At each visit, BCVA was determined and FFA or ICGA, CFP, and OCT were performed. Adverse effects reported by the patients were recorded. At baseline and at each follow-up visit systemic parameters ($HbA_{1C}$, serum glucose, serum creatinine, blood pressure) were evaluated.

## FFA and CFP grading

The comparison of OA values, FFA, and CFP was grouped into three categories:

1. ANG (−) / Vis (−): no leakage on FFA or ICG and funduscopical invisibility, indicating no induced treatment effect: "under-treatment".
2. ANG (+) / Vis (−): leakage on FFA or ICG, funduscopical invisibility: "desired SRT effect".
3. ANG (+) / Vis (+): leakage on FFA or ICG, funduscopical visibility, indicating undesired photoreceptor damage: "over-treatment".

CFP and FFA or ICG were evaluated by two independent, masked graders. Using CFP, the amount of hard exudates was evaluated and graded at 3 and 6 months follow-up and compared to baseline. Leakage in FFA or ICG was graded in a similar way. For the grading of both hard exudates and leakage, a continuous vertical scale was used (from −5 to +5) with the following instructions to the graders: "View the three randomly presented images labeled A, B, C and select the one that ranges in the middle in terms of damage. Draw a horizontal line through the continuous vertical scale at zero, and label the line as the middle image A, B, or C. Proceed to score the other two images with respect to the chosen middle image using a line and label it in the same way." Using this grading method, relative changes in CFP and FFA or ICG appearance from

baseline to 3 and 6 months were assessed, and thus the subjective impression was converted into an objective numerical scale. The agreement of the two graders reading was found to correlate significantly ($r$=0.54, $p$=0.0001).

### Retinal thickness

OCT analysis was performed using the in-built retinal thickness map software which calculates the average retinal thickness in nine areas, centered on the fovea. The average retinal thickness in the central area (1 mm diameter) (central retinal thickness) was evaluated at baseline and at 3- and 6-month follow-up. The area with the greatest baseline retinal thickness (maximum retinal thickness) was noted, and the retinal thickness in the same area was compared at 3- and 6-month follow-up.

### Statistical methods

In the statistical analysis of the main outcome measures the type I error (alpha) was set at 0.05. The paired $t$-test was used to calculate statistical significance of differences in BCVA, central retinal thickness, maximum retinal thickness, and systemic parameters during the study period. The Cohen's Kappa test was used to test the reproducibility of the gradings by two independent graders of CFP and FFA images. The correlation of the change of BCVA at the 3- and 6-month follow-up visits as compared to baseline with changes of the reduction of hard exudates, leakage on FFA, central retinal thickness, maximum retinal thickness, and HbA1c, serum glucose or serum creatinin at the corresponding time point was analyzed using the Pearson product-moment correlation coefficient ($r$). The results were statistically analysed using SPSS 15.0 software (SPSS Inc., Chicago, IL, USA).

## Results

### Patient data and applied laser parameters

Forty Caucasian patients participated in the study. One patient was excluded from the analysis because of study violation. The mean patient age was 63.9 years, standard deviation (SD)=9. Sixteen patients were female, 23 male. Of the patients, 91.1 % had type II diabetes, 8.9% type I diabetes. Retinopathy was classified as mild non-proliferative diabetic retinopathy (NPDR) according to the criteria of the ETDRS. SRT re-treatment was performed in 7/39 patients 3 months after the initial treatment. No complications or adverse effects were noted during or after SRT, and no patients reported any adverse effects related to SRT or pain during laser application. None of the laser lesions were funduscopically visible either 1 hour following laser treatment or at the subsequent follow-up visits. No signs of RPE change or atrophy was visible on slit-lamp bio-microscopy or on CFP at 6-month follow-up. The mean number of applied laser spots was 35.2 (SD=24, range 11–125). The mean treatment pulse energy was 247 µJ (SD=50, range 200–325).

### Primary outcome measure

#### Change of BCVA

Compared to baseline (43.7 letters (SD=9.1) mean BCVA remained unchanged at the 3-month follow-up (45.3 letters; SD=9.2, $p$=0.08). Mean BCVA had significantly improved from baseline to 46.1 letters (SD=10.5) at 6-month follow-up ($p$=0.02) (Fig. 3, Table 2). BCVA had improved (>5 letters gain) or remained stable (±5 letters) in 88% and 84% of eyes at the 3- and 6-month follow-up visits, respectively. Twelve percent and 16% of eyes had lost more than 5 letters at the 3- and 6-month follow-up visits respectively. In five of 39 patients (13%), BCVA had improved by ≥10 letters at the 6-month follow-up visit. BCVA had worsened by ≥10 letters in one patient (2.6 %) at the 6-month follow-up visit. No eyes had severe loss of vision (defined as a loss of ≥15 letters) at the 6-month follow-up visit.

### Other outcome measures

(1) Retinal thickness

At baseline, mean central retinal thickness was 276 µm (SD=118). Three months after treatment, mean central retinal thickness was 274 µm (SD=129), and 264 µm (SD=133) at the 6-month follow-up visit. The change of mean central retinal thickness at the 3- and 6-month follow-up visits was not statistically significant as compared to

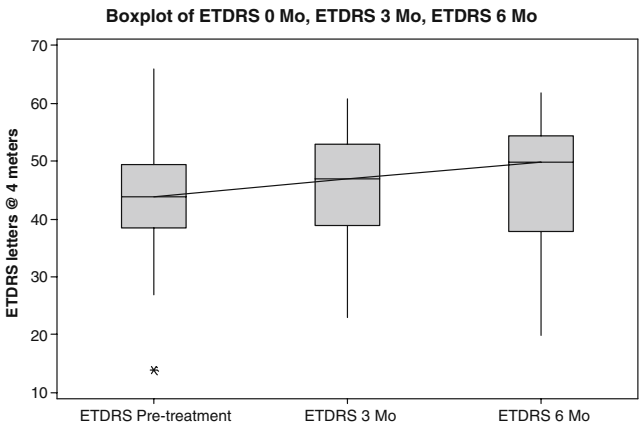


**Fig. 3** Boxplot of BCVA at baseline and 3 and 6 months after SRT. Mean BCVA improved from 43.7 letters (SD=9.1) at baseline to 46.1 letters (SD=10.5) at 6-month follow-up ($p$=0.02)

**Table 2** BCVA (best-corrected ETDRS visual acuity) , OCT center and maximum thickness of patients pre-treatment and at 3- and 6-month follow-up

| | BCVA | | | Central retinal thickness (μm) | | | Maximum retinal thickness (μm) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre | 3 months | 6 months | Pre | 3 months | 6 months | Pre | 3 months | 6 months |
| Mean | 43.7 | 45.3 | 46.1 | 276 | 274 | 264 | 383 | 381 | 370 |
| Standard deviation | 9.11 | 9.17 | 10.5 | 118 | 129 | 133 | 80 | 88 | 82 |
| *P*-value (*t*-test) | | 0.08 | 0.02 | | 0.46 | 0.18 | | 0.33 | 0.07 |
| No. of patients | 36 | 36 | 37 | 37 | 36 | 37 | 37 | 36 | 37 |

baseline ($p$=0.46 and $p$=0.18 respectively). Mean maximum retinal thickness was 383 μm (SD=80) at baseline, 381 μm (SD=88) after 3 months, and 370 μm (SD=82) after 6 months. The change of maximum retinal thickness at the 3- and 6-month follow-up visits was not statistically significant as compared to baseline ($p$=0.33 and $p$=0.07 respectively) (Table 2).

(2) Presence of hard exudates and leakage in FFA

Comparing pre- and post-treatment images, no statistically significant change of presence of hard exudates or leakage in FFA was found ($p$=0.88–0.99) (Table 3). Figure 4 shows an example of the disappearance of hard exudates in one eye 6 months after treatment compared to baseline.

(3) Accuracy of optoacoustic measurements in detecting the angiographic visible threshold of RPE effects.

The specificity of detecting the angiographic visible threshold was 86%, with a sensitivity of 70%. By doubling the OA value threshold, the specificity can be raised to 98% with a sensitivity of 68%. The OA value threshold for the angiographic leakage was 590 times smaller than the threshold for a visible effect (Fig. 2).

(4) Correlation of BCVA change with anatomical and systemic parameters.

Blood glucose levels were lower at the 6-month follow-up than at baseline ($p$=0.03). All other systemic parameters did not change significantly during the 6-month study period (Tables 4 and 5). There was a significant positive correlation between improvement of BCVA and a reduction of hard exudates (CFP) at both 3 months ($p$=0.03) and 6 months ($p$=0.01) after treatment. Improvement of BCVA correlated also with a reduction of central retinal thickness measured 6 months after treatment ($p$=0.01) (Fig. 5). There was no significant correlation between BCVA and leakage on FFA or maximum retinal thickness. There was also no correlation between BCVA and HbA1c, serum glucose, or serum creatinine (Table 6).

**Table 3** Unmasked color fundus photograph (CFP) and fundus fluorescein angiography (FFA) grading results pre-treatment and at 3- and 6-month follow up

| Grading type | Mean change | Standard deviation | *T*-test *p*-value |
|---|---|---|---|
| CFP 3 months | −0.67 | 1.57 | 0.99 |
| CFP 6 months | −0.50 | 1.43 | 0.88 |
| FFA 3 months | −0.50 | 1.28 | 0.99 |
| FFA 6 months | −0.47 | 1.12 | 0.96 |

## Discussion

There have been many advances in the management and understanding of diabetic eye disease, including glycemic,

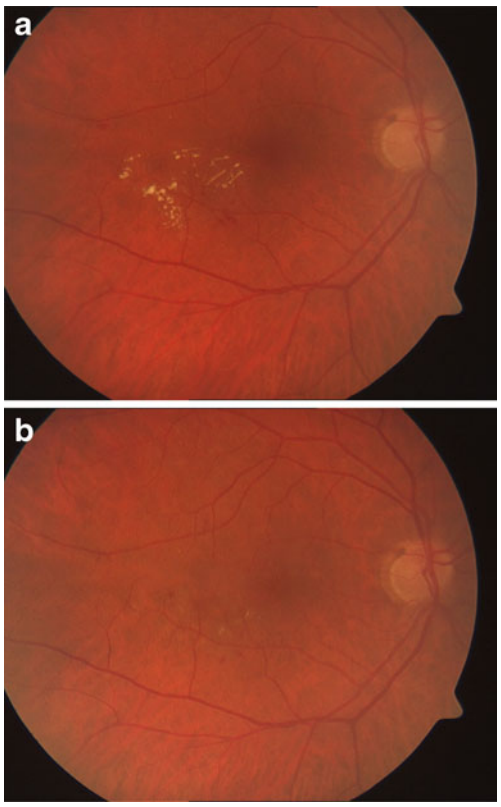


**Fig. 4** Color fundus photographs showing the reduction in hard exudates before (**a**) and 6 months (**b**) after SRT for DME. An obvious change in hard exudates can be noted

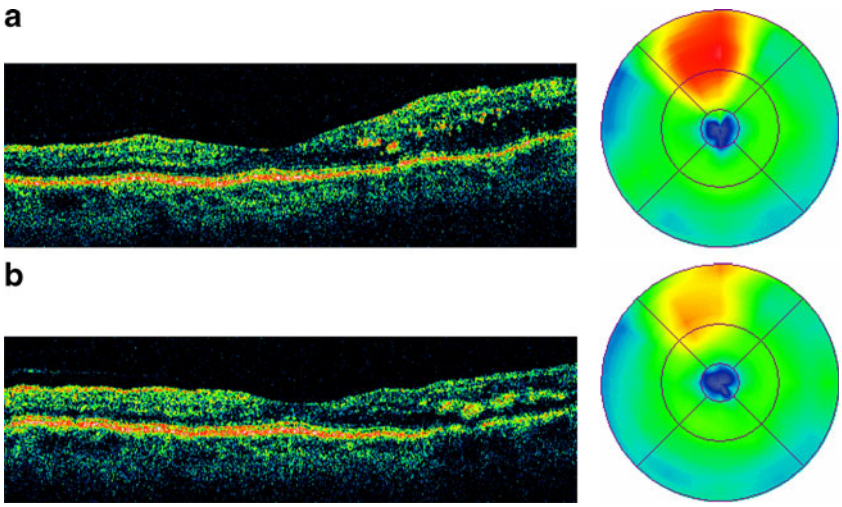


**Fig. 5** OCT scans showing the reduction of retinal thickness. **a** Vertical scan and retinal thickness map before SRT. **b** Vertical scan and retinal thickness map 6 months after SRT

blood pressure and serum lipid control to reduce the risk of onset and progression of diabetic retinopathy [5, 23, 24]. However, the exact pathogenesis of diabetic eye disease has not yet been fully elucidated. In DME, abnormal transduction of fluid and molecules into the retina is likely to occur due to increased hydrostatic forces transmitted to the capillaries and post-capillary venules governed by Starling's law [2, 25]. Compromise of vascular endothelial tight junctions also contributes to DME. Vascular endothelial tight junctions may be affected by VEGF and other cytokines which affect their function as a blood–retinal barrier [26]. Other contributing factors are altered oncotic pressure from hypoalbuminemia, hyperlipidemia, anemia, intravascular fluid overload, and poor blood glucose control [27]. The multifactorial pathogenesis of DME may be one reason why the therapeutic effect of the intravitreal application of steroids [7, 27] or anti-VEGF agents is often transient.

A dysfunction of the RPE pump has been described as a likely contributing factor of the abnormal intraretinal fluid accumulation in DME by decreasing the normal passage of fluid from the sensory retina towards the choriocapillaris [2, 12]. Therefore, a treatment that selectively stimulates RPE repair may significantly reduce DME. The ETDRS established the role of focal laser photocoagulation in preserving vision in patients diagnosed with "clinically significant macular edema" [6, 25]. More recent studies have additionally suggested a therapeutic effect of vitrectomy, especially for diffuse or refractory DME [28, 29]. However, at present conventional laser photocoagulation still represents the gold standard of treatment for DME [7]. Although the RPE is the primary site of laser absorption, conventional continuous wave green laser photocoagulation leads to heat conduction and irreversible thermal denaturation of the adjacent inner and outer photoreceptor segments [8]. This unwanted collateral damage may cause reduced visual acuity, loss of contrast sensitivity, and central scotoma, as well as patient discomfort or pain due to choroidal involvement during the actual treatment [30, 31]. Other, less frequent complications associated with conventional laser treatment are choroidal neovascularization [32] and subretinal fibrosis [33]. These limitations have led to the development of laser procedures that aim to minimize unnecessary tissue damage while preserving the therapeutic effect. We have previously shown the absence of microscotoma for up to 1 year following SRT in patients [21], and the actual treatment was painless in the present study. Postulated therapeutic mechanisms of RPE laser photocoagulation in DME include the spreading and migrating of the RPE cells at the edge of the laser site [34, 35] and the laser stimulation of RPE cell mitosis and repair [35, 36]. Modelling studies have shown that as opposed to contin-

**Table 4** HbA1c, glucose level and creatinin values of SRT patients pre-treatment and 3 and 6 months after treatment

| | HbA1c (%) | | | Glucose (mg/dl) | | | Creatinine (mg/dl) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre | 3 months | 6 months | Pre | 3 months | 6 months | Pre | 3 months | 6 months |
| Mean | 7.49 | 7.35 | 7.61 | 193 | 184 | 160 | 0.84 | 0.79 | 0.85 |
| STDV | 1.05 | 1.27 | 1.44 | 66.8 | 83.8 | 68.7 | 0.17 | 0.17 | 0.28 |
| *P*-value (*t*-test) | | 0.21 | 0.49 | | 0.57 | 0.03 | | 0.09 | 0.57 |
| No. of patients | 30 | 28 | 30 | 33 | 33 | 30 | 31 | 31 | 29 |

**Table 5** Systolic and diastolic blood pressure of patients pre-treatment and at 3- and 6-month follow-up

| | Blood pressure (mmHg) | | | | | |
|---|---|---|---|---|---|---|
| | Pre | | 3 months | | 6 months | |
| | Syst. | Diast. | Syst. | Diast. | Syst. | Diast. |
| Mean | 156 | 85 | 155 | 83 | 148 | 84 |
| Standard deviation | 21 | 13 | 21 | 13 | 22 | 11 |
| *P*-value (*t*-test) | | | 0.73 | 0.54 | 0.06 | 0.72 |
| No. of patients | 35 | 35 | 35 | 35 | 35 | 35 |

uous laser output, shorter pulse durations allow maximum thermal localization and selective tissue effects [9, 37]. Micropulse diode laser treatment (810 nm) uses a pulse duration of ~100 μs, and studies investigating its use in the treatment of DME show promising results, strengthening the idea that using reduced laser power selectively affecting the RPE may be all that is required to achieve a therapeutic effect in the treatment of DME [31, 38–42]. SRT has been developed to further improve selectivity by using a much shorter pulse duration of 1.7 μs, and consequently a higher irradiance. We have demonstrated in animal studies that selective treatment of the RPE is achieved using microsecond pulse durations, and the follow-up showed that the RPE regenerates with survival of the adjacent photoreceptors [9, 16, 43]. Moreover, the 527-nm green wavelength of the Nd:YLF laser is better absorbed by RPE melanosomes as compared to the infrared 810-nm light [44]. Less deep laser penetration into the surrounding tissue is associated with a lower risk of damage to Bruch's membrane and the choroid than lasers with longer wavelengths.

SRT could potentially be an effective and safe treatment of clinically significant DME, as in the present study functional and anatomical improvement or stabilization was achieved in 84% of patients. However, an adequately designed and adequately powered controlled phase III trial will be required to further test efficacy and safety of SRT as a treatment of DME. FFA is useful for the assessment of the permeability of the blood–retinal barrier, which is an important morphologic outcome measure of a treatment of DME [26]. However, it does not correlate with visual acuity after SRT, perhaps because FFA does not image the important fluid drainage into the choroid. Funduscopy is an important tool for the evaluation of the morphologic outcome, because following successful laser treatment, hard exudates are expected to significantly decrease. OCT has become an increasingly important and reproducible tool for quantitative assessment of macular edema [45, 46]. We found a significant correlation of improvement of BCVA and reduction of central retinal thickness; however, the overall results of the OCT measurements in the present study show that central retinal thickness was not significantly reduced at the 6-month follow-up. This is in accordance with the findings of other patient studies reporting an only-moderate reduction of retinal thickness after laser treatment, ranging from 0% to 20% 6 months after treatment [47, 48]. Therefore, while focal laser treatment for DME has been shown to effectively prevent severe visual loss [6, 25] retinal thickness may not be an ideal parameter for monitoring the therapeutic effect.

The functional results of the present study are comparable to other laser studies [49]. Olk described an average improvement of visual acuity by 17 % 6 months after treatment with a conventional argon laser [49].

The number of applied spots to focal areas of leakage was chosen according to our clinical experience with the

**Table 6** *R* of the ETDRS letter results difference after 3 months and 6 months respectively, relative to the other measures of differences for this study at the same time point

| Pearson product moment | BCVA | | BCVA | |
|---|---|---|---|---|
| Correlation coefficient and probability | 3 months vs 0 months | | 6 months vs 0 months | |
| | *R* | *P*-value | *R* | *P*-value |
| Angiographic leakage | 0.11 | 0.35 | 0.05 | 0.66 |
| Color fundus photo | 0.26 | 0.03 | 0.29 | 0.01 |
| Central retinal thickness | 0.20 | 0.23 | −0.44 | 0.01 |
| Maximum retinal thickness | 0.25 | 0.14 | −0.31 | 0.06 |
| HbA1c | −0.11 | 0.58 | −0.01 | 0.99 |
| Glucose | −0.07 | 0.69 | −0.02 | 0.93 |
| Creatinin | −0.04 | 0.83 | −0.08 | 0.69 |

use of a conventional laser. While it was not the aim of the present study to determine the ideal number of laser spots required to achieve an optimal therapeutic effect, the therapeutic effect could possibly be enhanced by fewer or more applied SRT laser spots.

Compared to conventional laser treatment, the application of SRT may require more experience, because the laser spots are not funduscopically visible during treatment, and care must be taken not to re-treat previous spots. However, we were able to treat focal areas of leakage in all patients with the pulse energy appropriate for the individual patient.

The analysis of the optoacoustic measurements was reliable for dosimetry, with a specificity of 86 %. The correlation of RPE damage determined by FFA with the detection of micro-bubbles has previously been demonstrated in patients by using the optoacoustic technique [19]. Thus, in further studies it may be possible to omit FFA. With careful assessment of the pulse energy needed to ensure photoreceptor-sparing treatment, SRT can be applied close to the fovea. Treatment spots can be applied with a low risk of compromising visual acuity or inducing central scotomas by direct photoreceptor damage or as a result of subsequent enlargement of a laser burn, as frequently observed after conventional laser treatment. Therefore, SRT could potentially be applied earlier than recommended by the ETDRS guidelines and earlier treatment may improve long-term functional outcomes.

## Conclusion

SRT appears to be safe. The present results shows that SRT could be an effective treatment for DME. Mean BCVA improved and, overall, BCVA was stabilized or improved in 84% of patients 6 months after SRT. The absence of collateral damage in the neural retina and the choroid makes SRT particularly useful as a treatment of central edema close to or within the foveal avascular zone. A prospective controlled randomized patient study comparing conventional laser photocoagulation with SRT as a treatment of DME is required.

## Outlook

At present, conventional laser treatment of DME is often carried out at a relatively advanced stage of the disease, when some degree of visual loss has already occurred. As the resolution of imaging tools such as OCT continues to improve, mild DME may be detected at an earlier stage. Because of the selective effect on the RPE sparing the photoreceptors, SRT is a suitable candidate for treatment of DME at an earlier stage, before irreversible neuroretinal damage has occurred. Additionally, SRT and anti-VEGF therapy could be combined to achieve synergistic therapeutic effects.

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