A Review of Subthreshold Micropulse Laser for Treatment of Macular Disorders

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ABSTRACT

Micropulse laser treatment is an alternative to the conventional continuous-wave laser for the treatment of retinal or macular diseases. In contrast to the conventional laser, the therapeutic effect of the subthreshold micropulse laser is not accompanied by thermal retinal damage. This fact is of particular importance when a treatment near the fovea is required. Micropulse treatment is applied in indications such as central serous chorioretinopathy (CSC), diabetic macular edema (DME), or macular edema due to retinal vein occlusion (RVO). This review outlines and discusses the published literature of subthreshold micropulse laser treatment for CSC, DME, and macular edema after RVO.

Keywords: Central serous chorioretinopathy; Diabetic macular edema; Micropulse laser; Ophthalmology; Retinal vein occlusion; Subthreshold laser

INTRODUCTION

Traditional laser photocoagulation has been used to treat different retinal diseases for many years [1–5]. Here, the endpoint is a visible whitening of the retina due to thermal damage of the retinal pigment epithelium (RPE) and the inner retina. However, apart from the favored therapeutic effect, the treatment can lead to undesirable side effects like visual field defects, epiretinal fibrosis, and choroidal neovascularization (CNV) in the area of the laser scar [6–10]. The mechanisms which are responsible for the therapeutic effect are still poorly understood.

Scarring seems not to be necessary to achieve a therapeutic effect. It might be the stimulation of the RPE alone and not the destroying of the photoreceptors that is needed to reach a therapeutic effect of laser photocoagulation [11]. The laser energy stimulates the RPE, which leads to repair of the inner blood retinal barrier [12]. A modification of the gene expression initiated by the wound healing response after laser photocoagulation could be responsible for the beneficial effect of laser photocoagulation. Sublethally injured RPE cells induce an up- and downregulation of various factors [pigment epithelium-derived factor (PEDF), vascular endothelial growth factor (VEGF) inhibitors,
VEGF inducers, permeability factors, etc.] which restores the pathologic imbalance. RPE cells destroyed by thermal heat are not capable of inducing this biologic activity [13, 14]. Inagaki et al. [15] showed that sublethal photothermal stimulation with a micropulse laser induces heat shock protein expression in RPE cells without cellular damage in a model of human RPE.

In subthreshold micropulse laser (SML), diffusion of heat to surrounding tissues is minimized and thereby scarring is prevented.

The neural retina can be spared by applying the minimum laser irradiance (watts per square meter) needed to raise the temperature of the RPE, but without exceeding the protein denaturation threshold. This leads to the required activation of the RPE cells, but the thermal wave will only reach the neural retina at temperatures beneath the protein denaturation threshold. Since the RPE and the neural retina are close together, the laser pulse has to be in the microsecond range and not in the millisecond range like the traditionally used supra threshold laser. For safety reasons it is not possible to deliver the required energy in one short enough laser pulse. A single laser pulse would require so much energy that there would be a high risk of bubble formation and micro-explosions, accompanied by retinal hemorrhages [16]. Those side effects can be avoided by using a repetitive series of very short pulses with low energy instead of a continuous-wave laser pulse [17–19].

The micropulse operating mode and terminology were described by Dorin [20]. In the traditional continuous-wave mode, a single laser pulse of 0.1–0.5 s delivers the preset laser energy. In the micropulse mode, a train of repetitive short laser pulses delivers the laser energy within an “envelope” whose width is typically 0.1–0.5 s. The normal length of each pulse is 100–300 μs. The “envelope” includes “ON” time, which is the duration of each micropulse, and “OFF” time, which is the time between the micropulses. The “OFF” time is important since here the originated heat can cool down. The sum of the “ON” and “OFF” times is the period T and its reciprocal 1/T is the frequency (pulses per second) f in hertz (Hz).

The duty cycle in percent is the ratio between “ON” time and the period T.

DIFFERENT LASERS AVAILABLE WITH MICROPULSE MODE

810-nm Diode Laser

The commercially available diode lasers emit at a wavelength of 810 nm, which is in the near-infrared range of the spectrum. A feature of the 810-nm wavelength is its deep penetration into the choroid, but it is not clear if this characteristic is relevant in micropulse treatment. For all indications requiring a treatment near the foveal avascular zone, the 810-nm laser has the advantage that the laser energy will relatively spare the inner neurosensory retina and affect mainly the deeper layers [21–24]. The deep penetration is a possible benefit especially for central serous chorioretinopathy (CSC) since the choroid may play a role in the pathogenesis of CSC. A potential disadvantage of the 810-nm laser is a possible sensation of pain during treatment with a diode laser [24, 25], although this is a rare problem in the micropulse mode.

577-nm Yellow Laser

Another laser type which is available for micropulse treatment is the 577-nm yellow laser. The yellow laser has the advantage that xanthophyll, the pigment which is located in the inner and outer plexiform layers of the macula, absorbs the yellow light only minimally so treatment near the fovea is relatively safe [26].

APPLICATIONS FOR SUBTHRESHOLD MICROPULSE LASERS

In this article we will review the applications for micropulse laser in macular diseases, namely CSC, diabetic macular edema (DME), and retinal vein occlusion (RVO). We will give an overview of the available literature and outline
the current evidence for micropulse laser treatment in each field.

The literature search was performed in English language in the PubMed database. We used pairings of the terms “micropulse”, “laser”, “subthreshold”, and “central serous chorioretinopathy”, “chorioretinopathy”, “central serous retinopathy”, or “diabetic macular edema”, “macular edema” and “retinal vein occlusion”, “branch retinal vein occlusion”, “central retinal vein occlusion”. Additionally, the references of the resultant articles were checked for publications missing in the primary search. Until February 2017 we found 18 articles [27–44] concerning micropulse laser in CSC; no articles were excluded and all articles are listed in Table 1. As a result of the high number of publications related to DME and micropulse treatment, we only listed the 11 prospective studies [45–55] in Table 2. We found four studies [56–59] investigating micropulse laser for RVO, which are all listed in Table 3.

As a result of different study designs, uneven inclusion and exclusion criteria, different laser types, treatment parameters, and various outcome measures, a direct comparison of the studies is limited. We looked for similarities referring to the outcome measures for making comprehensive conclusions regarding the treatment outcome. In Tables 1, 2, and 3, all studies are listed, but individual studies were excluded from the calculations as a result of missing information or prior treatment. The studies had a high variety regarding the follow-up visits. If available, after calculation of the decrease in central retinal thickness (CRT) in optical coherence tomography (OCT) in all individual studies, a weighted average value was calculated on the basis of the number of patients in each study. The best corrected visual acuity (BCVA) was not consistently presented in the different studies. To compare the BCVA, we converted all visual acuity data to Early Treatment Diabetic Retinopathy Study (ETDRS) letters equivalent using the formula ETDRS letters = 85 + 50 × log (Snellen fraction) [60]. If a large enough number of studies provided information about a control group, we additionally analyzed the control group regarding CRT, BCVA, and treatment outcome.

This article was based on previously conducted studies and did not involve any new studies of human or animal subjects performed by any of the authors.

CENTRAL SEROUS CHORIORETINOPATHY (CSC)

In CSC a serous detachment of the neurosensory retina leads to decreased vision [61]. The acute form of CSC is often self-limiting so that treatment is not always necessary. But some patients develop the chronic form of CSC with impending permanent structural damage and vision loss [62–64]. For patients with extrafoveal leakage, a continuous-wave laser photocoagulation is a treatment option. Studies showed an acceleration of subretinal fluid (SRF) resolution but no change in final visual acuity or recurrence rate after conventional laser. Furthermore, adverse events like CNV, scotomas, enlargement of the laser spot, and reduction of contrast sensitivity can occur [3, 62, 65–67]. Another treatment option is photodynamic therapy (PDT) which is used also in juxtafoveal or subfoveal leakage. But even with reduced treatment settings, complications like RPE atrophy, choroidal hypoperfusion, transient reduction of macular function, and CNV can occur [68–71].

Bandello et al. [72] presented the first pilot study investigating SML treatment for CSC in 2003. They reported a high treatment success with complete resorption of SRF in five out of five eyes within 1 month and no recurrence of SRF during follow-up of 2–6 month after non-visible subthreshold micropulse diode laser (810 nm) treatment. No evidence of RPE or retinal changes was discernible at fluorescein angiography (FA) or fundus biomicroscopy after laser treatment.

Table 1 shows all identified studies investigating micropulse laser treatment for CSC. In Table 4, the treatment outcome after SML, PDT, and observation for CSC is presented.

Treatment Response

Most studies defined a treatment response as a reduction in CRT measured in spectral domain...
| Authors       | Year | Eyes | Disease duration | Laser type and parameters | Study design                                           |
|--------------|------|------|------------------|---------------------------|-------------------------------------------------------|
| Ricci et al. | 2004 | 1 eye| Chronic, ≥6 months | Iris Medical Oculight SLx 810 nm, Ø not shown, 10% DC, 0.5 s, power: 500 mW | Case report, SML after ICG injection                  |
| Ricci et al. | 2008 | 7 eyes| Chronic, ≥6 months | Iris Medical Oculight SLx 810 nm, Ø 112.5 μm, 10% DC, 0.5 s, power: 500 mW | Prospective, interventional, non-comparative case series, SML after ICG injection |
| Chen et al.  | 2008 | 26 eyes | Chronic, >4 months | Iris Medical Oculight SLx 810 nm, Ø 125 μm, 15% DC, 0.2 s, power: titration | Prospective, non-comparative, interventional case series |
| Lanzetta et al. | 2008 | 24 eyes | Chronic, >3 months | Iris Medical Oculight SLx 810 nm, Ø 200 μm, 15% DC, 0.2 s, power: 1000–2000 mW, mean 1350 mW | Prospective, interventional, non-comparative case series |
| Gupta et al. | 2009 | 5 eyes | Chronic, ≥4 weeks | Iris Medical Oculight SLx 810 nm, Ø 125 μm, 15% DC, 0.2 s, power: titration | Retrospective, non-comparative, case series |
| Koss et al.  | 2011 | 52 eyes | Chronic, >3 months | Iris Medical Oculight SLx 810 nm, Ø 125 μm, 15% DC, 0.2 s, power: titration | Prospective, comparative, nonrandomized interventional case series |
| Roisman et al. | 2013 | 15 eyes | Chronic, >6 months | Opto FastPulse 810 nm, Ø 125 μm, 15% DC, 0.3 s, power: 1.2× threshold | Prospective, randomized, double-blind, sham-controlled pilot trial, cross over after 3 months |
| Malik et al. | 2015 | 11 eyes | Chronic, >3 months | Iris Medical Oculight SLx 810 nm, Ø not shown, 5% DC, 0.2–0.3 s, power: 750–1000 mW | Retrospective, interventional, non-comparative case series |
| Kretz et al. | 2015 | 62 eyes | Chronic, >3 months | Iris Medical Oculight SLx 810 nm, Ø 75–125 μm, 15% DC, 0.3 s, power: average 1500 mW | Prospective, randomized, interventional, comparative trial |
| Authors        | Year | Eyes | Disease duration     | Laser type and parameters                      | Study design                      |
|---------------|------|------|----------------------|------------------------------------------------|-----------------------------------|
| Elhamid [36]  | 2015 | 15   | Chronic, >3 months   | Iridex IQ577                                    | Prospective, interventional, non-comparative clinical study |
|               |      |      |                      | 577 nm, Ø 200 µm, 10% DC, 0.2 s, power: titration |                                   |
| Scholz et al. [37] | 2015 | 38   | Chronic, >6 weeks    | Quantel Medical Supra Scan                       | Retrospective, non-comparative case series |
|               |      |      |                      | 577 nm, Ø 160 µm, 5% DC, 0.2 s, power: 50% of threshold |                                   |
| Kim et al. [38] | 2015 | 10   | Chronic, >6 months   | Quantel Medical Supra Scan                       | Retrospective, non-comparative case series |
|               |      |      |                      | 577 nm, Ø 100 µm, 15% DC, 0.2 s, power: 50% of threshold |                                   |
| Gawecki [39]  | 2015 | 1    | Chronic, (disease duration not defined) | Model not mentioned                              | Retrospective case report |
|               |      |      |                      | 577 nm, Ø 160 µm, 5% DC, 0.2 s, power: 550 mW   |                                   |
| Yadav et al. [40] | 2015 | 15   | Chronic, >3 months   | Quantel Medical Supra Scan                       | Retrospective, non-comparative case series |
|               |      |      |                      | 577 nm, Ø 100 µm, 10% DC, 0.2 s, power: 50% of threshold |                                   |
| Breukink et al. [41] | 2016 | 59   | Chronic, (disease duration not defined) | Iris Medical Oculight SLx                        | Prospective, interventional non-comparative case series |
|               |      |      |                      | 810 nm, Ø 125 µm, 5% DC, 0.2 s, power: ≤1800 mW |                                   |
| Ozmert et al. [42] | 2016 | 33   | Chronic, >6 months   | Quantel Medical Supra Scan                       | Retrospective, comparative case series |
|               |      |      |                      | 577 nm, Ø 160 µm, 5% DC, 0.2 s, power: titration |                                   |
| Ambiya et al. [43] | 2016 | 10   | ≥3 months without signs of RPE atrophy or diffuse leakage | Navilas                                        | Prospective, interventional nonecomparative case series |
|               |      |      |                      | 577 nm, Ø 100 µm, 5% DC, 0.1 s, power: 30% of threshold |                                   |
| Scholz et al. [44] | 2016 | 100  | Chronic, ≥6 weeks    | Quantel Medical Supra Scan                       | Retrospective, comparative, interventional case series |
|               |      |      |                      | 577 nm, Ø 160 µm, 5% DC, 0.2 s, power: 50% of threshold |                                   |
| Authors            | FU               | Treatment response                                                                 | Central retinal thickness | Best corrected visual acuity | Safety                                                                 | Laser sessions |
|--------------------|------------------|------------------------------------------------------------------------------------|---------------------------|------------------------------|------------------------------------------------------------------------|----------------|
| Ricci et al. [27]  | 8 weeks          | 1 week: SRF was reduced (1/1)                                                      | Not shown                 | BL: 0.3 logMAR               | No signs of laser treatment were visible on FA                         | 1              |
|                    |                  | 8 weeks: Complete resolution (1/1)                                                 |                           | 1 week: 0.0 logMAR           |                                                                        |                |
|                    | Minimum 12 months | Response*: 2 weeks: 7/7 (100%)                                                    | Not shown                 | 8 weeks: −0.1 logMAR         | No laser lesions were visible via funduscopic examination and on FA    | 1              |
|                    |                  | 8 weeks: 7/7 (100%)                                                               |                           |                              |                                                                        |                |
|                    |                  | Complete*: 5/7 (71%)                                                              |                           |                              |                                                                        |                |
|                    |                  | *12 months: no recurrence in patients with complete resolution of SRF. No worsening of SRF in patients with incomplete recovery |                           |                              |                                                                        |                |
| Chen et al. [29]   | Minimum 6 months | FFU response:                                                                      |                           |                              |                                                                        |                |
|                    | (9.5 ± 2.6 months) | Group 1: 6/6 (100%)                                                               | Group 1:                  |                              |                                                                        |                |
|                    |                  | Group 2: 8/9 (89%)                                                               | Group 2:                  |                              |                                                                        |                |
|                    |                  | Group 3: 5/11 (46%)                                                              | Group 3:                  |                              |                                                                        |                |
|                    |                  | All eyes: 19/26 (73%)                                                           | All eyes: 19/26 (73%)     |                              |                                                                        |                |
|                    |                  | FFU complete:                                                                     | FFU complete:             |                              |                                                                        |                |
|                    |                  | Group 1: 6/6 (100%)                                                               | Group 1:                  |                              |                                                                        |                |
|                    |                  | Group 2: 8/9 (89%)                                                               | Group 2:                  |                              |                                                                        |                |
|                    |                  | Group 3: 5/11 (46%)                                                              | Group 3:                  |                              |                                                                        |                |
|                    |                  | All eyes: 19/26 (73%)                                                           | All eyes: 19/26 (73%)     |                              |                                                                        |                |
|                    |                  | Significant CRT decrease in all patients (p < 0.001)                             |                          |                              |                                                                        |                |
| Lanzetta et al. [30]| 3–36 months (mean 14 months) | Response:                                                                         | BL: 328 μm (range 162–720 μm) | BL: 20/32 Snellen            | −5/24 eyes showed RPE changes at the site of SML spots                 | 1–5            |
|                    |                  | 1 month: 16/24 (67%)                                                            | 1 month: 197 μm (range 93–403 μm) | 1 month: 20/25 Snellen       |                                                                        |                |
|                    |                  | FFU: 18/24 (75%)                                                                | FFU: 168 μm (range 107–340 μm) | FFU: 20/25 Snellen           |                                                                        |                |
|                    |                  | Complete:                                                                        |                            |                              |                                                                        |                |
|                    |                  | 1 month: 9/24 (38%)                                                             |                            |                              |                                                                        |                |
|                    |                  | FFU: 17/24 (71%)                                                                |                            |                              |                                                                        |                |

**Note:** CRT = Central Retinal Thickness; BCVA = Best Corrected Visual Acuity; FA = Fluorescein Angiography; SRF = Subretinal Fluid; FFU = Follow-up.
| Authors          | FU       | Treatment response                        | Central retinal thickness | Best corrected visual acuity | Safety                                                                 | Laser sessions |
|------------------|----------|-------------------------------------------|---------------------------|------------------------------|-------------------------------------------------------------------------|----------------|
| Gupta et al.     | Minimum  | FU response: 5/5 (100%)                   | Not shown                 | Improvement in BCVA in all patients | No complications mentioned                                              | 1–2            |
|                  | 6 months | FU complete: 4/5 (80%)                    |                           |                              |                                                                         |                |
| Koss et al.      | 10 months| FU response: not shown                    |                           |                              |                                                                         | 1–3            |
|                  |          | FU complete: not shown                    |                           |                              |                                                                         |                |
|                  |          | Leakage activity in FA                   |                           |                              |                                                                         |                |
|                  |          | 10 months                                 |                           |                              |                                                                         |                |
|                  |          | SML: 2/16 (12.5%)                         |                           |                              |                                                                         |                |
|                  |          | BCZ: 6/10 (60%)                           |                           |                              |                                                                         |                |
|                  |          | Observation: 24/26 (92%)                 |                           |                              |                                                                         |                |
|                  |          | SML leads to significantly more leakage activity reduction than BCT $p = 0.00239$ and observation $p = 0.0054$ |                           |                              |                                                                         |                |
| Roisman et al.   | Minimum  | Not shown                                 |                           |                              |                                                                         | 1–2            |
|                  | 6 months |                                |                           |                              |                                                                         |                |
|                  |          | SML:                                      |                           |                              |                                                                         |                |
|                  |          | BL: 419 ± 59 μm                          |                           |                              |                                                                         |                |
|                  |          | 6 weeks: 387 ± 94 μm                     |                           |                              |                                                                         |                |
|                  |          | 6 months: 329 ± 69 μm                    |                           |                              |                                                                         |                |
|                  |          | 10 months: 325 ± 93 μm                   |                           |                              |                                                                         |                |
|                  |          | BCZ:                                      |                           |                              |                                                                         |                |
|                  |          | BL: 393 ± 84 μm                          |                           |                              |                                                                         |                |
|                  |          | 6 weeks: 355 ± 114 μm                    |                           |                              |                                                                         |                |
|                  |          | 6 months: 334 ± 59 μm                    |                           |                              |                                                                         |                |
|                  |          | 10 months: 355 ± 73 μm                   |                           |                              |                                                                         |                |
|                  |          | Observation:                             |                           |                              |                                                                         |                |
|                  |          | BL: 388 ± 59 μm                          |                           |                              |                                                                         |                |
|                  |          | 6 weeks: 396 ± 57 μm                     |                           |                              |                                                                         |                |
|                  |          | 6 months: 388 ± 63 μm                    |                           |                              |                                                                         |                |
|                  |          | 10 months: 415 ± 53 μm                   |                           |                              |                                                                         |                |
|                  |          | Significant decrease in CRT at 3 months after SML $p = 0.0098$ but not after BCZ or observation $p = 0.0054$ |                           |                              |                                                                         |                |
|                  |          | SML better than BCZ $p = 0.00047$ and observation $p = 0.0054$ at 10 months |                           |                              |                                                                         |                |
|                  |          | No laser scars observed at funduscopic examination or on FA |                           |                              |                                                                         |                |
| Authors            | FU                | Treatment response | Central retinal thickness | Best corrected visual acuity | Safety                                                                 | Laser sessions |
|--------------------|-------------------|--------------------|--------------------------|------------------------------|------------------------------------------------------------------------|----------------|
| Malik et al.       | Minimum 2 months  | FU response: 8/11  | BL: 414 ± 137 μm         | BL: 39.2 ± 15.1 ETDRS        | No evidence of RPE damage in FAF or in FA                              | 1–2           |
|                    | (2–12 months)     | (72%)              | FFU: 316 ± 97 μm         | FFU: 45.5 ± 12 ETDRS         |                                                                        |                |
|                    |                   | FU complete: not   | Significant CRT decrease |                             |                                                                        |                |
|                    |                   | shown              | after SML (p = 0.0046)    |                             |                                                                        |                |
| Kretz et al.       | 4 months          | 4-month response   | Change BL/4 months:      | Change BL/4 months:         | No evidence of secondary RPE damage in FAF after both treatments       | 1–3           |
|                    |                   | (reduction of     | SML: -69.7 μm            | SML: +6.7 ETDRS             |                                                                        |                |
|                    |                   | leakage activity): | HD PDT: -109.8 μm        | HD PDT: +8.5 ETDRS           |                                                                        |                |
|                    |                   | SML: 12/20 (60%)   | Observation: -89 μm      | Observation: +1.5 ETDRS      |                                                                        |                |
|                    |                   | HD PDT: 16/24 (67%)|                          |                             |                                                                        |                |
|                    |                   | Observation: 7/18  |                          |                             |                                                                        |                |
|                    |                   | (38%)              |                          |                             |                                                                        |                |
| Elhamid            | 6 months          | Response:          | BL: 390 ± 46 μm          | BL: 0.67 ± 0.10 Snellen      | No sign of laser-induced lesions                                      | 1–2           |
|                    |                   | 3 months: 15/15     | 6 months: 264 ± 24 μm    | 6 months: 0.85 ± 0.10 Snellen|                                                                        |                |
|                    |                   | (100%)             | Significant CRT decrease | Significant BCVA increase    |                                                                        |                |
|                    |                   | Complete:          | after SML (p < 0.05)     | after SML (p < 0.05)         |                                                                        |                |
|                    |                   | 3 months: 11/15     |                          |                             |                                                                        |                |
|                    |                   | (73%)              |                          |                             |                                                                        |                |
|                    |                   | 6 months: 13/15     |                          |                             |                                                                        |                |
|                    |                   | (86%)              |                          |                             |                                                                        |                |
| Scholz et al.      | Minimum 6 weeks   | Response:          | BL: 402 ± 139 μm         | BL: 0.36 ± 0.24 logMAR       | No laser burns were detected with any imaging modality                 | 1–3           |
|                    | (mean 5 ± 3 months)| 6 weeks: 24/38     | 6 weeks: 309 ± 86 μm     | 6 weeks: 0.33 ± 0.24 logMAR  |                                                                        |                |
|                    |                    | (63%)              | FFU: 287 ± 75 μm         | FFU: 0.30 ± 0.25 logMAR      |                                                                        |                |
|                    |                    | 3 months: 20/23     | Significant CRT decrease | Significant BCVA increase    |                                                                        |                |
|                    |                    | (87%)              | after SML (p < 0.001)    | after SML (p = 0.039)        |                                                                        |                |
|                    |                    | 6 months: 11/14     |                          |                             |                                                                        |                |
|                    |                    | (79%)              |                          |                             |                                                                        |                |
|                    |                    | FFU: 28/38          |                          |                             |                                                                        |                |
|                    |                    | (74%)              |                          |                             |                                                                        |                |
|                    |                    | Complete:          |                          |                             |                                                                        |                |
|                    |                    | 6 weeks: 5/38       |                          |                             |                                                                        |                |
|                    |                    | (13%)              |                          |                             |                                                                        |                |
|                    |                    | 3 months: 7/23      |                          |                             |                                                                        |                |
|                    |                    | (30%)              |                          |                             |                                                                        |                |
|                    |                    | 6 months: 2/14      |                          |                             |                                                                        |                |
|                    |                    | (14%)              |                          |                             |                                                                        |                |
|                    |                    | FFU: 9/38           |                          |                             |                                                                        |                |
Table 1 continued

| Authors       | FU            | Treatment response                                                                 | Central retinal thickness     | Best corrected visual acuity                | Safety                                                                 | Laser sessions |
|---------------|---------------|-------------------------------------------------------------------------------------|-------------------------------|---------------------------------------------|-------------------------------------------------------------------------|-----------------|
| Kim et al.    | Minimum       | There were 2 patients who had recurrent CSC. One at 6 months, one at 10 months. One patient had persistent SRF for 3 months despite total of 4 laser sessions | BL: 349 ± 53 μm 3 months: 251 ± 29 μm FFU: 261 ± 38 μm Significant CRT decrease at 3 months (p = 0.009) and FFU (p = 0.009) | BL: 0.21 ± 0.21 logMAR 3 months: 0.06 ± 0.09 logMAR FFU: 0.04 ± 0.06 logMAR Significant BCVA increase at 3 months (p = 0.020) and FFU (p = 0.012) | No laser scar was detected in color fundus photographs, SDOCT, or near-infrared images | 1–5             |
| Gawecki [39]  | Not specified | Response: 0/1 After 1st treatment: no change After 2nd treatment: ‘significant amount of SRF present in the macular area’ | BL: 0.63 decimal FU 1st*: no change FU 2nd*: 0.32 decimal treatment* |                                       | FAF showed hyperfluorescent punctate areas referring to multispot SML pattern | 2               |
| Yadav et al.  | Minimum       | FU: CRT not shown SRF (high): BL: 232 μm FU: 49 μm Significant decrease in SRF (p < 0.001) |                                       | Change: 1 line BL: 20/40 Snellen FU: 20/30 Snellen Significant BCVA increase (p = 0.015) | No evidence of RPE or retinal damage on SDOCT, FA, or on FAF | 1               |
| Breukink et al. | 8–118 weeks  | After mean 8.7 weeks, (range: 4–18 weeks) Complete after: 1st HdPDT: 37/59 (63%) 2nd HdPDT: 7/19 (37%) 1st SML: 1/10 (10%) | Not shown | BL (all): 0.28 logMAR FFU (all): 0.16 logMAR | No difference in eyes after HdPDT or SML | 1–2 HdPDT 1 SML |
| Özmert et al. | Minimum       | SML: Response: 13/15 (87%) Complete: 12/15 (80%) HiPDT: Response: 14/18 (78%) Complete: 13/18 (72%) | SML: BL: 287.3 ± 126 μm 12 months: 138.0 ± 40 μm HiPDT: BL: 242.8 ± 80 μm 12 months: 156.9 ± 60 μm Significant CRT decrease after SML (p = 0.003), but not after HiPDT (p = 0.098) | SML: BL: 67.3 ± 14.2 ETDRS 12 months: 71.5 ± 21.4 ETDRS | No visible retinal scarring | 1–2 SML |

Note: FU = follow-up; CRT = central retinal thickness; SRF = subretinal fluid; BCVA = best corrected visual acuity; Laser sessions refer to the number of laser treatments used.
| Authors                  | FU     | Treatment response | Central retinal thickness | Best corrected visual acuity | Safety                                                                 | Laser sessions |
|--------------------------|--------|--------------------|---------------------------|-----------------------------|-------------------------------------------------------------------------|-----------------|
| Ambiya et al. [43]       | 6 months | Response:          | BL: 298 ± 129 μm          | BL: 73.3 ± 16.1 ETDRS       | No evidence of laser spots via funduscopic examination, on SDOCT, and on FAF | 1–2            |
|                          |        | 1 month: 10/10     | 1 month: 200 ± 72 μm      | 1 month: 73.1 ± 16.3 ETDRS  | No complications                                                         |                 |
|                          |        | Complete:          | 3 months: 179 ± 53 μm     | 3 months: 75.8 ± 14.0 ETDRS |                                                                         |                 |
|                          |        | 1 month: 4/10 (40%) | 6 months: 215 ± 90 μm     | 6 month: 76.9 ± 13.0 ETDRS  |                                                                         |                 |
|                          |        | 3 month: 6/10 (60%) | Significant CRT decrease at 6 months (p = 0.03) | No significant increase in BCVA (p = 0.59) |                                                                         |                 |
|                          |        | 6 months: 6/10 (60%) |                           |                             |                                                                         |                 |
| Scholz et al. [44]       | 6 weeks | SML 6 weeks:       | SML:                      | SML:                        | No laser spots detectable by funduscopic examination or on FA           | 1              |
|                          |        | Response: 33/42     | BL: 445 ± 153 μm          | BL: 0.39 ± 0.24 logMAR      |                                                                         |                 |
|                          |        | (79%)               | 6 weeks: 297 ± 95 μm      | 6 weeks: 0.31 ± 0.27 logMAR |                                                                         |                 |
|                          |        | Complete: 15/42 (36%) | HdpDPT;                 | HdpDPT;                     |                                                                         |                 |
|                          |        | HdpDPT 6 weeks:    | BL: 398 ± 88 μm          | BL: 0.35 ± 0.24 logMAR      |                                                                         |                 |
|                          |        | Response: 34/58     | 6 weeks: 322 ± 93 μm      | 6 weeks: 0.31 ± 0.24 logMAR |                                                                         |                 |
|                          |        | (59%)               | Significant decrease in both groups (SML: p < 0.001, hdpDPT: p < 0.001) CRT decrease better after SML (p = 0.041) | |                                                                         |                 |
|                          |        | Complete: 12/58 (21%) |                            |                             |                                                                         |                 |
|                          |        | SML showed higher treatment response than HdpDPT (p = 0.036) | |                             |                                                                         |                 |

*BCVA* best corrected visual acuity, *BCZ* bevacizumab (intravitreal), *BL* baseline, *CRT* central retinal thickness, *CSC* central serous chorioretinopathy, *DC* duty cycle, *ETDRS* Early Treatment Diabetic Retinopathy Study Group letters, *FA* fluorescein angiography, *FAF* fundus autofluorescence, *FU* follow-up, *FFU* final follow-up, *HdpDPT* half dose photodynamic therapy, *HpDPT* half fluence photodynamic therapy, *ICG* indocyanin green, *IOP* intraocular pressure, *logMAR* logarithm of the minimum angle of resolution, *OCT* optical coherence tomography, *RPE* retinal pigment epithelium, *SDOCT* spectral domain OCT, *SML* subthreshold micropulse laser, *SRF* subretinal fluid, *Ø* spot size
| Authors       | Year | Eyes | Inclusion criteria | Laser type and parameters | Study design                                      |
|--------------|------|------|--------------------|---------------------------|---------------------------------------------------|
| Fazel et al. [45] | 2016 | 68   | DME*               | Quantel Medical           | Prospective, single-blind, randomized clinical trial |
|              |      |      | SML: n = 34        | 810 nm, Ø 50–100 μm, 0.1 s, power: adjusted |                                                  |
|              |      |      | CL: n = 34         | Quantel Medical           |                                                  |
|              |      |      | CRT <450 μm        |                           |                                                  |
|              |      |      | Without PDR        |                           |                                                  |
|              |      |      | Without previous IVT or any retinal laser |                           |                                                  |
| Inagaki et al. [46] | 2015 | 53   | DME*, type II      | Iris Medical IQ577        | Prospective, non-randomized, interventional case series |
|              |      |      | 810 nm: n = 24     | 577 nm, Ø 200 μm          | Additional micro-aneurysm closure in both groups at BL |
|              |      |      | 577 nm: n = 29     | 15% DC, 0.2 s, power: 2x threshold, (mean 204 mW) |                                                  |
|              |      |      | No IVT or laser within the last 3 months |                           |                                                  |
|              |      |      | Patients with isolated local FA dye were excluded |                           |                                                  |
| Vujosevic et al. [47] | 2015 | 53   | DME* <400 μm, type I/II diabetes | Iris Medical IQ577        | Prospective, masked, randomized, comparative pilot study |
|              |      |      | 810 nm: n = 27     | 577 nm, Ø 100 μm, 5% DC, 0.2 s, power: 250 mW, HD treatment |                                                  |
|              |      |      | 577 nm: n = 26     | Iris Medical OcuLight SLX, 810 nm, Ø 200 μm, 15% DC, 0.2 s, power: 750 mW, HD treatment |                                                  |
| Othman et al. [48] | 2014 | 220  | DME* without PDR and foveal ischemia | Iris Medical OcuLight SLX 810 nm, Ø 75–125 μm, 15% DC, 0.3 s, power: 650–1000 mW confluent | Prospective, single-center, nonrandomized, interventional case series |
|              |      |      | Group 1 Primary treatment (n = 187) |                           |                                                  |
|              |      |      | Group 2 Secondary treatment (n = 33) |                           |                                                  |
|              |      |      | Group 1 without prior treatment, BCVA at least 20/80 |                           |                                                  |
|              |      |      | Group 2 with prior CL, BCVA at least 20/200 |                           |                                                  |
| Authors                  | Year | Eyes  | Inclusion criteria                              | Laser type and parameters                                                                 | Study design                              |
|--------------------------|------|-------|-------------------------------------------------|------------------------------------------------------------------------------------------|------------------------------------------|
| Venkatesh et al. [49]    | 2011 | 46 eyes | DME* without PDR                                | Iris Medical                                                                              | Prospective, randomized interventional study |
|                          |      |       | SML: $n = 23$                                   |                                                                                           |                                          |
|                          |      |       | CL: $n = 23$                                    |                                                                                           |                                          |
|                          |      |       | No prior medical or laser treatment within the last 6 months |                                                                                           |                                          |
| Lavinsky et al. [50]     | 2011 | 123 eyes | DME* with CRT $\geq 250 \mu m$                    | Opto FastPulse                                                                            | Prospective, randomized, controlled, double-masked clinical trial |
|                          |      |       | ND-SLM: $n = 39$                                |                                                                                           |                                          |
|                          |      |       | HD-SLM: $n = 42$                                |                                                                                           |                                          |
|                          |      |       | CL: $n = 42$                                    |                                                                                           |                                          |
|                          |      |       | No prior macular laser or IVT for DME            | 810 nm, $\Omega 125 \mu m$, 15% DC, 0.3 s                                                   |                                          |
|                          |      |       | No panretinal laser within last 4 months         | 0.3 s, power: 1.2× threshold                                                               |                                          |
|                          |      |       |                                          | ND-SML: 2 invisible burn widths apart                                                      |                                          |
|                          |      |       |                                          | HD-SML: Confluent invisible burn                                                           |                                          |
|                          |      |       |                                          | Iridex, Nd:YAG LC                                                                          |                                          |
|                          |      |       |                                          | 532 nm, $\Omega 75 \mu m$, 0.05–0.1 s, power: titration                                  |                                          |
|                          |      |       |                                          | mETDRS grid                                                                                |                                          |
| Ohkoshi and Yamaguchi [51]| 2010 | 43 eyes | DME* with CRT $\leq 600 \mu m$ without PDR      | Iris Medical                                                                              | Prospective, nonrandomized interventional study |
|                          |      |       | Type II                                         | OcuLight SLX                                                                               |                                          |
|                          |      |       | Patients with isolated local FA dye were excluded| 810 nm, $\Omega 200 \mu m$, 15% DC, 0.2–0.3 s                                               |                                          |
|                          |      |       | No prior medical or laser treatment within last 6 months | power: 520–100 mW confluent                                                                 |                                          |
| Nakamura et al. [52]     | 2010 | 28 eyes | DME*                                            | Iris Medical                                                                              | Prospective                               |
|                          |      |       | No prior laser or surgical therapy within last 6 months | OcuLight SLX                                                                               |                                          |
|                          |      |       |                                               | 810 nm, $\Omega 200 \mu m$, 15% DC, 0.2 s, power: titrated, grid pattern was used           |                                          |
| Authors          | Year | Eyes  | Inclusion criteria                                                                 | Laser type and parameters                                                                 | Study design                                                                 |
|-----------------|------|-------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Vujosevic et al. [53] | 2010 | 62 eyes | DME*, type II <br>No prior medical/laser/surgical treatment within last 6 months | Coherent Novus Omni laser, 514 nm, Ø 100 μm, 0.1 s power: 80–100 mW mETDRS grid CL Iris Medical OcuLight SLX 810 nm, Ø 125 μm 5% DC, 0.2 s, power: 750 mW | Prospective, randomized clinical trial (retreatment after 3 months if: CMT ≥ 250 μm or CMT reduction ≤ 50% or BCVA decrease >5 ETDRS letters) |
| Figueira et al. [54] | 2009 | 84 eyes | Both eyes DME*, type II, <80 years without PDR <br>No prior laser treatment | Iridex Oculite GLx argon green 514 nm, Ø 100–200 μm 0.1 s, power: titration Iris Medical OcuLight SLX 810 nm, Ø 125 μm 15% DC, 0.3 s, power: titration | Prospective, randomized, controlled, double-masked trial |
| Laursen et al. [55] | 2004 | 23 eyes | DME* without PDR <br>Without prior LC <br>Without retinal surgery | Iris Medical OcuLight SLX 810 nm, Ø 125 μm 5% DC, 0.1 s, power: titration Novus 200 argon green | Prospective, randomized |

| Authors          | FU (months) | Central retinal thickness         | Best corrected visual acuity | Safety | Additional treatments |
|-----------------|-------------|----------------------------------|-------------------------------|--------|-----------------------|
| Fazel et al. [45] | 4           | 810 nm SML: 810 nm SML:          | BL: 0.59 ± 0.3 logMAR         | No laser scars after SML | Laser scars after CL |
|                 |             | BL: 373 ± 56 μm 4 months:        | 4 months: 0.52 ± 0.3 logMAR   |        | Not mentioned         |
|                 |             | 810 nm CL: 810 nm CL:            | BL: 355 ± 53 μm 4 months:    |        |                       |
|                 |             | SML superior to CL               | 4 months: 0.60 ± 0.3 logMAR   |        |                       |
|                 |             | (p = 0.001; 4 months)            | SML superior to CL            | (p = 0.015; 4 months) |                       |
| Authors                  | FU (months) | Central retinal thickness | Best corrected visual acuity | Safety                                      | Additional treatments          |
|-------------------------|-------------|---------------------------|-------------------------------|---------------------------------------------|--------------------------------|
| Inagaki et al. [46]     | 12          | 810 nm:                   | 810 nm:                       | No laser scars in either group              | 810 nm: 12.5% Re-SML, 4.2% IVT |
|                         |             | BL: 488 ± 176 µm          | BL: 0.59 ± 0.41 logMAR        |                                             | (bevacizumab)                  |
|                         |             | 3 months: 404.5 µm        | 3 months: 0.57 logMAR         |                                             | 5–577 nm: 3.4% Re-SML          |
|                         |             | 6 months: 394.4 µm        | 6 months: 0.53 logMAR         |                                             |                                |
|                         |             | 12 months: 361.8 µm       | 12 months: 0.54 logMAR        |                                             |                                |
|                         |             | 577 nm:                   | 577 nm:                       |                                             |                                |
|                         |             | BL: 417 ± 113 µm          | BL: 0.31 ± 0.31 logMAR        |                                             |                                |
|                         |             | 3 months: 345.8 µm        | 3 months: 0.32 logMAR         |                                             |                                |
|                         |             | 6 months: 340.6 µm        | 6 months: 0.32 logMAR         |                                             |                                |
|                         |             | 12 months: 335.2 µm       | 12 months: 0.28 logMAR        |                                             |                                |
|                         |             | No significant difference | BCVA stable in both groups, intergroup differences were not evaluated |                                             |                                |
| Vujosevic et al. [47]   | 6           | 810 nm:                   | 810 nm:                       | No laser scars or visible secondary effects of laser spots in either group | 810 nm: 85.2% Re-SML, 5–577 nm: 88.5% Re-SML |
|                         |             | BL: 340 ± 36 µm           | BL: 78.6 ± 7.5 ETDRS          |                                             |                                |
|                         |             | 6 months: 335 ± 55 µm     | 3 months: 79.3 ± 6.8 ETDRS    |                                             |                                |
|                         |             | 577 nm:                   | 6 months: 77.3 ± 8.2 ETDRS    |                                             |                                |
|                         |             | BL: 358 ± 46 µm           | 577 nm:                       |                                             |                                |
|                         |             | 6 months: 340 ± 56 µm     | BL: 79.7 ± 6.1 ETDRS          |                                             |                                |
|                         |             | Significant decrease for 577 nm group at 6 months \(p = 0.009\) and not for 810 nm \(p = 0.45\) | 3 months: 79.4 ± 7.6 ETDRS | No significant difference of BCVA between groups at 3 months \(p = 0.3\) and at 6 months \(p = 0.62\) | 5–577 nm: 88.5% Re-SML          |
Table 2 continued

| Authors               | FU (months) | Central retinal thickness | Best corrected visual acuity | Safety                                                                 | Additional treatments                  |
|-----------------------|-------------|---------------------------|------------------------------|------------------------------------------------------------------------|----------------------------------------|
| Othman et al. [48]    | 12          | 810 nm: Primary treatment (1) | 810 nm: primary treatment (1) | Laser marks seen as pigmenatry changes were noted 3.3% via funduscope examination and 5.7% via FA | Group 1: 23% Re-SML (median 2 × SML) 11.7% IVT (triamcinolone) 3.2% ppV Group 2: 33% IVT (triamcinolone) |
|                       |             | BL: 353 ± 80 μm           | BL: 0.21 logMAR               |                                                                        |                                        |
|                       |             | 4 months: 257 ± 51 μm     | 4 months: 0.15 logMAR         |                                                                        |                                        |
|                       |             | 12 months: 215 ± 27 μm    | 12 months: 0.18 logMAR        |                                                                        |                                        |
|                       |             | 810 nm: Secondary treatment (2) | 810 nm: secondary treatment (2) |                                                                        |                                        |
|                       |             | BL: 429 ± 69 μm           | BL: 0.50 logMAR               |                                                                        |                                        |
|                       |             | 4 months: 356 ± 64 μm     | 4 months: 0.44 logMAR         |                                                                        |                                        |
|                       |             | 12 months: 263 ± 59 μm    | 12 months: 0.46 logMAR        |                                                                        |                                        |
|                       |             | In both groups, CRT decrease was significant at 4 and 12 months (p < 0.05) | In group 1, BCVA improved at 4 months (p = 0.017) and was stable at 12 months for 85% of the eyes In group 2, no significant BCVA change was observed |                                                                        |                                        |
| Venkatesh et al. [49] | 6           | 810 nm SML:               | 810 nm SML:                  |                                                                        |                                        |
|                       |             | BL: 299 ± 50 μm           | BL: 0.41 ± 0.3 logMAR         |                                                                        |                                        |
|                       |             | 3 months: 287 ± 53 μm     | 3 months: 0.41 ± 0.3 logMAR   |                                                                        |                                        |
|                       |             | 6 months: 275 ± 63 μm     | 6 months: 0.43 ± 0.3 logMAR   |                                                                        |                                        |
|                       |             | 532 nm YAG CL:            | 532 nm YAG CL:               |                                                                        |                                        |
|                       |             | BL: 313 ± 47 μm           | BL: 0.33 ± 0.2 logMAR         |                                                                        |                                        |
|                       |             | 3 months: 296 ± 34 μm     | 3 months: 0.36 ± 0.2 logMAR   |                                                                        |                                        |
|                       |             | 6 months: 287 ± 33 μm     | 6 months: 0.41 ± 0.3 logMAR   |                                                                        |                                        |
|                       |             | No difference between SML and CL (p = 0.064) | No difference between SML and CL (p = 0.77) for BCVA. Better preservation of retinal sensitivity in SML group |                                                                        |                                        |
|                       |             | 810 nm SML:               | 810 nm SML:                  |                                                                        |                                        |
|                       |             | 4/23 eyes with focal void regions | 532 nm YAG-CL: 18/23 eyes with focal void regions |                                                                        |                                        |
|                       |             | In mfERG:                 | Not mentioned                |                                                                        |                                        |
| Authors | FU (months) | Central retinal thickness | Best corrected visual acuity | Safety | Additional treatments |
|---------|-------------|---------------------------|-----------------------------|--------|----------------------|
| Lavinsky et al. [50] | 12 | 810 nm ND-SML: 379 (279–619) μm | 810 nm ND-SML: 0.70 (0.4–1.3) logMAR | SML: No laser scars or visible laser burns after SML, although some very light laser-induced lesions could be identified | 810 nm ND-SML: 21% re-SML (once) |
| | | 3 months: 332 (223–610) μm | 3 months: 0.80 (0.4–1.3) logMAR | | 77% Re-SML (twice) |
| | | 6 months: 316 (215–627) μm | 6 months: 0.80 (0.4–1.3) logMAR | | |
| | | 12 months: 311 (207–599) μm | 12 months: 0.80 (0.3–1.3) logMAR | CL: laser scars after CL | 810 nm HD-SML: 38% Re-SML (once) |
| | 810 nm HD-SML: | 810 nm HD-SML: 371 (297–879) μm | 810 nm HD-SML: 0.90 (0.3–1.3) logMAR | | 13% Re-SML (twice) |
| | | 3 months: 301 (203–698) μm | 3 months: 0.70 (0.2–1.3) logMAR | | 532 nm CL: |
| | | 6 months: 291 (201–577) μm | 6 months: 0.60 (0.2–1.3) logMAR | | 32% Re-CL (once) |
| | | 12 months: 226 (187–513) μm | 12 months: 0.52 (0.2–1.3) logMAR | | 24% Re-CL (twice) |
| | 532 nm YAG mETDRS CL: | 532 nm YAG mETDRS CL: | 532 nm YAG mETDRS CL: 810 nm HD-SML: 0.80 (0.3–1.3) logMAR | | |
| | | BL: 370 (269–710) μm | BL: 0.80 (0.3–1.3) logMAR | | |
| | | 3 months: 306 (209–512) μm | 3 months: 0.75 (0.3–1.3) logMAR | | |
| | | 6 months: 290 (208–501) μm | 6 months: 0.70 (0.2–1.3) logMAR | | |
| | | 12 months: 249 (199–475) μm | 12 months: 0.65 (0.3–1.3) logMAR | | |
| | HD-SML, CL were superior to ND-SLM group (p < 0.001) | HD-SML with significant BCVA increase | HD-SML with significant BCVA increase 12 months (p = 0.009). | No difference between ND-SLM and CL group: No improvement | |
| | No difference between HD-SLM and CL groups (p = 0.75) | No difference between HD-SLM and CL groups (p = 0.75) | No difference between HD-SLM and CL groups (p = 0.75) | No difference between HD-SLM and CL groups (p = 0.75) | |
| Ohkoshi and Yamaguchi [51] | 12 | 810 nm SML: 342 ± 119 μm | 810 nm SML: 0.12 ± 0.2 logMAR | No laser scars, no evidence of laser treatment | 19% re-SML (once) |
| | | 3 months: 301 ± 124 μm | 3 months: 0.12 ± 0.2 logMAR | After 1 year, one patient showed pigmentary changes | 7% 1 × grid CL |
| | | 6 months: 292 ± 122 μm | 6 months/12 months: N/A | | 2% CL of microaneurysm |
| | | 12 months: 290 ± 123 μm | Stable BCVA until 12 months | | 2% IVT |
| | | CRT reduction was significant at 3 months (p = 0.05) and stable afterwards | CRT reduction was significant at 3 months (p = 0.05) and stable afterwards | | 4% ppV |
| Authors                  | FU (months) | Central retinal thickness       | Best corrected visual acuity       | Safety                                                                 | Additional treatments                                                                 |
|-------------------------|-------------|---------------------------------|-----------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Nakamura et al. [52]    | 3           | 810 nm SML, CFT changes:        | 810 nm SML                        | No laser scars, no evidence of laser treatment                          | Not mentioned                                                                         |
|                         |             | BL: 481 ± 110 μm                 | BL: 0.47 ± 0.2 logMAR              |                                                                         |                                                                                        |
|                         |             | 3 months: 388 ± 127 μm           | 3 months: 0.40 ± 0.2 logMAR        |                                                                         |                                                                                        |
|                         |             | Significant CFT reduction at     | Significant BCVA improve at 3      |                                                                         |                                                                                        |
|                         |             | 3 months (p = 0.004)             | months (p = 0.03)                 |                                                                         |                                                                                        |
| Vujosevic et al. [53]   | 12          | 810 nm SML:                     | 810 nm SML:                       | SML: No signs of laser treatment via funduscopic examination and on FA | Number of treatments: SML: 2.03 ± 0.75                                                 |
|                         |             | BL: 358 ± 94 μm                  | BL: 0.21 ± 0.30 logMAR             |                                                                         | CL: 2.10 ± 1.0                                                                         |
|                         |             | 3 months: 341 ± 114 μm           | 3 months: 0.23 ± 0.29 logMAR       |                                                                         |                                                                                        |
|                         |             | 6 months: 346 ± 113 μm           | 6 months: 0.24 ± 0.32 logMAR       |                                                                         |                                                                                        |
|                         |             | 12 months: 312 ± 76 μm           | 12 months: 0.24 ± 0.25 logMAR      |                                                                         |                                                                                        |
|                         |             | 514 nm argon CL:                 | 514 nm argon CL:                  |                                                                         |                                                                                        |
|                         |             | BL: 378 ± 95 μm                  | BL: 0.29 ± 0.30 logMAR             |                                                                         |                                                                                        |
|                         |             | 3 months: 338 ± 72 μm            | 3 months: 0.32 ± 0.33 logMAR       |                                                                         |                                                                                        |
|                         |             | 6 months: 327 ± 77 μm            | 6 months: 0.29 ± 0.27 logMAR       |                                                                         |                                                                                        |
|                         |             | 12 months: 310 ± 87 μm           | 12 months: 0.30 ± 0.30 logMAR      |                                                                         |                                                                                        |
|                         |             | No significant difference between | No significant difference between   |                                                                         |                                                                                        |
|                         |             | CL and SML                       | CL and SML                       |                                                                         |                                                                                        |
|                         |             |                                |                                   |                                                                         |                                                                                        |
| Figueira et al. [54]    | 12          | 810 nm SML:                     | 810 nm SML:                       | SML: 13.9% of the treated eyes showed laser scars                     | Not mentioned                                                                         |
|                         |             | BL: 249 ± 59 μm                  | BL: 78.4 ± 8.1 ETDRS              |                                                                         |                                                                                        |
|                         |             | 12 months: 291 ± 104 μm          | 12 months: 71.8 ETDRS             |                                                                         |                                                                                        |
|                         |             | 514 nm Argon CL:                 | 514 nm argon CL:                  |                                                                         |                                                                                        |
|                         |             | BL: 255 ± 62 μm                  | BL: 78.0 ± 7.8 ETDRS              |                                                                         |                                                                                        |
|                         |             | 12 months: 284 ± 105 μm          | 12 months: 70.70 ETDRS            |                                                                         |                                                                                        |
|                         |             | No significant differences between CL and SML (p = 0.81) | No significant differences between CL and SML (p = 0.88) |                                                                         |                                                                                        |
| Authors          | FU (months) | Central retinal thickness | Best corrected visual acuity | Safety                                      | Additional treatments |
|------------------|-------------|---------------------------|------------------------------|---------------------------------------------|-----------------------|
| Laursen et al. [55] | 5–8         | Focal LC/diffuse LC       | BL BCVA cannot be extracted! | No laser complications were observed in both groups | Not mentioned         |
|                  |             | Central retinal thickness |                              |                                             |                       |
|                  |             | 810 nm SML focal LC (n = 6) | 3 months: +2.8 ETDRS         |                                             |                       |
|                  |             | BL: 275 µm                |                              |                                             |                       |
|                  |             | 3 months: 250 µm          |                              |                                             |                       |
|                  |             | 6 months: 256 µm          |                              |                                             |                       |
|                  |             | 810 nm SML diffuse LC (n = 6) | 6 months: +3.5 ETDRS         |                                             |                       |
|                  |             | BL: 293 µm                |                              |                                             |                       |
|                  |             | 3 months: 318 µm          |                              |                                             |                       |
|                  |             | 6 months: 341 µm          |                              |                                             |                       |
|                  |             | 514 nm Argon focal LC (n = 5) | 3 months: +4.6 ETDRS         |                                             |                       |
|                  |             | BL: 325 µm                |                              |                                             |                       |
|                  |             | 3 months: 338 µm          |                              |                                             |                       |
|                  |             | 6 months: 330 µm          |                              |                                             |                       |
|                  |             | 514 nm Argon diffuse LC (n = 6): | 6 months: +0.6 ETDRS        |                                             |                       |
|                  |             | BL: 272 µm                |                              |                                             |                       |
|                  |             | 3 months: 308 µm          |                              |                                             |                       |
|                  |             | 6 months: 90 µm           |                              |                                             |                       |
| In all patients with focal edema CRT decrease significant (p = 0.02) |          |                           |                              |                                             |                       |

* BL baseline, CL conventional laser, CRT central retinal thickness, DC duty cycle, DME diabetic macular edema, ETDRS Early Treatment Diabetic Retinopathy Study Group letters, EA fluorescein angiography, FU follow-up, HD-SLM high density subthreshold micropulse laser, logMAR logarithm of the minimum angle of resolution, IVT intravitreal drug therapy, mfERG multifocal electroretinography, mETDRS modified ETDRS (Early Treatment Diabetic Retinopathy Study Group) Grid, ND-SLM normal density subthreshold micropulse laser, NdYAG neodymium–yttrium–aluminum garnet laser, PDR proliferative diabetic retinopathy, ppV pars plana vitrectomy, OCT optical coherence tomography, SML subthreshold micropulse laser, Ø spot size

* Clinically significant DME
Table 3 Overview of the studies investigating subthreshold micropulse laser treatment for macular edema after branch retinal vein occlusion

| Authors          | Year | Eyes | Inclusion criteria                                      | Laser type and parameters                               | Study design                                      |
|------------------|------|------|---------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------|
| Parodi et al.    | 2015 | 35   | ME to due BRVO                                          | Iris Medical                                           | Prospective, randomized, interventional           |
|                  |      |      | CFT > 250 μm                                            | OcuLight SLX 810 nm, Ø 125 μm, 15% DC, 0.3 s, power:   |                                                   |
|                  |      |      | Without non-perfusion ≥ 5 disc areas                    | titration                                             |                                                   |
|                  |      | Group 1: SML: n = 18                                   |                                                        |                                                       |
|                  |      | Group 2: IVT Bevacizumab (PRN after 3 initial injections)|                                                        |                                                       |
|                  |      | n = 17                                               |                                                        |                                                       |
|                  | 2014 | 32   | ME due to BRVO (ischemic/ non-ischemic)                 | Iris Medical                                           | Retrospective, single-center, nonrandomized,     |
|                  |      |      | CRT <600 μm                                             | OcuLight SLX, 810 nm, Ø 200 μm, 15% DC, 0.2 or 0.3 s, | interventional case series                       |
|                  |      |      | No prior macular therapy (LC, IVT etc.) within last 6   | Power: 750–1500 mW (90%) for 0.2 s or 360–2000 mW      |
|                  |      |      | months                                                 | (60%) for 0.3 s                                        |
|                  |      | Group 1: BCVA ≤20/40                                  |                                                        |                                                       |
|                  |      | n = 15                                               |                                                        |                                                       |
|                  |      | Group 2: BCVA >20/40                                  |                                                        |                                                       |
|                  |      | n = 17                                               |                                                        |                                                       |
| Parodi et al.    | 2008 | 24   | ME due to BRVO                                          | Iris Medical                                           | Prospective randomized pilot clinical trial       |
|                  |      |      | CRT >212 μm                                            | OcuLight SLX, 810 nm Ø 125 μm, 15% DC, 0.3 s, power:  |
|                  |      |      | No prior laser treatment                                | titration                                             |                                                   |
|                  |      |      | Without non-perfusion ≥ 5 disc areas                    |                                                        |                                                   |
|                  |      | Group 1: SML only                                    |                                                        |                                                       |
|                  |      | n = 13                                               |                                                        |                                                       |
|                  |      | Group 2: SML + IVT Triamcinolone                       |                                                        |                                                       |
|                  |      | n = 11                                               |                                                        |                                                       |
| Parodi et al.    | 2006 | 36   | ME due to BRVO                                          | Iris Medical                                           | Prospective, randomized clinical trial           |
|                  |      |      | CRT >210 μm                                            | OcuLight SLX 810 nm Ø 125 μm, 10% DC, 0.2 s, power:   |
|                  |      |      | No prior laser treatment                                | titration                                             |                                                   |
|                  |      |      | Without non-perfusion ≥ 5 disc areas                    |                                                        |                                                   |
|                  |      | Group 1: SML grid                                    |                                                        |                                                       |
|                  |      | n = 17                                               |                                                        |                                                       |
|                  |      | Group 2: Krypton grid                                 |                                                        |                                                       |
|                  |      | n = 19                                               |                                                        |                                                       |
| Authors          | FU (months) | Central retinal thickness | Best corrected visual acuity | Safety        | Additional treatments |
|------------------|-------------|---------------------------|------------------------------|---------------|-----------------------|
| Parodi et al.    | 12          | SML group (CFT):          |                              |               |                       |
|                  |             | BL: 485.5 μm              | SML group:                   | No laser scars| Not mentioned         |
|                  |             | 3 months: 472.0 μm        | BL: 0.92 logMAR              |               |                       |
|                  |             | 6 months: 475.0 μm        | 3 months: 0.89 logMAR        |               |                       |
|                  |             | 9 months: 475.0 μm        | 6 months: 0.89 logMAR        |               |                       |
|                  |             | 12 months: 445.0 μm       | 9 months: 0.94 logMAR        |               |                       |
|                  |             | IVT group (CFT):          | 12 months: 0.99 logMAR       |               |                       |
|                  |             | BL: 484.2 μm              | IVT group:                   |               |                       |
|                  |             | 3 months: 305.0 μm        | BL: 0.94 logMAR              |               |                       |
|                  |             | 6 months: 266.0 μm        | 3 months: 0.88 logMAR        |               |                       |
|                  |             | 9 months: 265.0 μm        | 6 months: 0.88 logMAR        |               |                       |
|                  |             | 12 months: 271.0 μm       | 9 months: 0.85 logMAR        |               |                       |
|                  |             | IVT group significantly better (p = 0.001) | | | |
| Inagaki et al.   | 12          | Group 1: (BCVA ≤ 20/40 Snellen) | Group 1: (BCVA ≤ 20/40 Snellen) | No laser scars | Group 1: | |
|                  |             | BL: 409.3 μm              | BL: 0.59 logMAR              |               | Group 1: | n = 8 (53.3%) |
|                  |             | 1 month: 394.3 μm         | 1 month: 0.54 logMAR         |               | Group 2: | n = 3 (17.6%) |
|                  |             | 3 months: 371.3 μm        | 3 months: 0.54 logMAR        |               |           | |
|                  |             | 6 months: 313.5 μm        | 6 months: 0.58 logMAR        |               |           | |
|                  |             | 12 months: 303.5 μm       | 12 months: 0.51 logMAR       |               |           | |
|                  |             | Group 2: (BCVA > 20/40 Snellen) | Group 2: (BCVA > 20/40 Snellen) |               |           | |
|                  |             | BL: 373.3 μm              | BL: 0.13 logMAR              |               |           | |
|                  |             | 1 month: 353.5 μm         | 1 month: 0.09 logMAR         |               |           | |
|                  |             | 3 months: 313.1 μm        | 3 months: 0.13 logMAR        |               |           | |
|                  |             | 6 months: 294.1 μm        | 6 months: 0.09 logMAR        |               |           | |
|                  |             | 12 months: 320.1 μm       | 12 months: 0.12 logMAR       |               |           | |
|                  |             | Significant CRT decrease at 3, 6, and 12 months for both groups. No significant difference between the groups at any time point | | | |

[56] [57]
| Authors          | FU (months) | Central retinal thickness | Best corrected visual acuity | Safety | Additional treatments |
|------------------|-------------|---------------------------|------------------------------|--------|-----------------------|
| **Parodi et al.** | 12          | SML only:                 | SML only:                    | No     | Not mentioned         |
|                  |             | BL: 429 μm                | BL: 0.76 logMAR              |        |                       |
|                  |             | 3 months: 364 μm          | 3 month: 0.78 logMAR         |        |                       |
|                  |             | 6 months: 320 μm          | 6 months: 0.78 logMAR        |        |                       |
|                  |             | 9 months: 290 μm          | 9 months: 0.73 logMAR        |        |                       |
|                  |             | 12 months: 278 μm         | 12 months: 0.65 logMAR       |        |                       |
|                  |             | SML + IVT (triamcinolone):| SML + IVT (triamcinolone):   |        |                       |
|                  |             | BL: 476 μm                | BL: 0.67 logMAR              |        |                       |
|                  |             | 3 months: 269 μm          | 3 months: 0.50 logMAR        |        |                       |
|                  |             | 6 months: 276 μm          | 6 months: 0.45 logMAR        |        |                       |
|                  |             | 9 months: 260 μm          | 9 months: 0.36 logMAR        |        |                       |
|                  |             | 12 months: 283 μm         | 12 months: 0.35 logMAR       |        |                       |
|                  |             | Combined SML + IVT showed | Combined SML + IVT showed     | No     |                       |
|                  |             | better response at 3 months | significant better response at 9th and 12th months (p < 0.001) |     |                       |
|                  |             | (p < 0.001). No difference | groups |     |                       |
|                  |             | between groups from 9th month on | (p < 0.009, p = 0.011, respectively) | | |
| **Parodi et al.** | 24          | SML grid:                 | SML grid:                    | No     | Not mentioned         |
|                  |             | BL: 480 μm                | BL: 0.70 logMAR              |        |                       |
|                  |             | 6 months: 457 μm          | 6 months: 0.70 logMAR        |        |                       |
|                  |             | 12 months: 217 μm         | 9 months: 0.55 logMAR        |        |                       |
|                  |             | 18 months: 215 μm         | 12 months: 0.51 logMAR       |        |                       |
|                  |             | 24 months: 208 μm         | 24 months: 0.49 logMAR       |        |                       |
|                  |             | Krypton grid:             | Krypton grid:                | No     |                       |
|                  |             | BL: 454 μm                | BL: 0.69 logMAR              |        |                       |
|                  |             | 6 months: 252 μm          | 6 months: 0.60 logMAR        |        |                       |
|                  |             | 12 months: 226 μm         | 9 months: 0.58 logMAR        |        |                       |
|                  |             | 18 months: 229 μm         | 12 months 0.57 logMAR        |        |                       |
|                  |             | 24 months: 217 μm         | 24 m: 0.56 logMAR            |        |                       |
|                  |             | Krypton showed better response at 3 months and 6 months (p < 0.001). SML showed better response from 12th month on (p < 0.001) | | | |

BRVO branch retinal vein occlusion, BL baseline, CFT central foveal thickness, CRT central retinal thickness, DC duty cycle, FA fluorescein angiography, IVT intravitreal drug therapy, logMAR logarithm of the minimum angle of resolution, ME macular edema, PRN pro re nata, SML subthreshold micropulse laser
OCT (SDOCT). A complete resolution of SRF in SDOCT was defined as a complete treatment response. Two studies measured the leakage activity in FA as a parameter for treatment response [32, 35]. For simplicity reasons we do not distinguish between the different definitions for treatment response in our calculations. Few studies did not mention the amount of patients with treatment response. If we were able to work out the treatment response from the data shown in the paper, we quote the response; otherwise the studies were excluded [33, 38]. One case report was excluded from the calculation because of prior bevacizumab treatment [39], and two studies were excluded since they included patients with prior PDT [37, 41]. Few studies mentioned only the response or the complete response, and those studies were included in the calculations.

We included 191 patients from 12 studies for the calculations of the treatment response and 176 patients from 11 studies for the complete response. A total of 156 (79.6%) of the 191 patients showed a treatment response at the last mentioned follow-up: 112 (63.6%) of the 176 patients had a complete resolution of SRF. Only two studies showed data concerning the improvement rate in an untreated control group: a complete resolution of SRF was seen in 2 (8%) out of 26 eyes at the last follow-up and a reduction in SRF in 7 (39%) out of 18 eyes.

Four studies had a control group consisting of patients receiving PDT treatment (half dose PDT in three studies and half fluence PDT in one). The treatment response could be calculated from 100 patients in three studies and the complete treatment response from 135 patients in three studies. A total of 64 (64%) of the 100 patients responded to PDT and 62 (46%) of 135 patients showed complete response.

Safety

The majority of studies described no visible retinal changes after the micropulse laser treatment. In six patients from two studies [30, 39] pigmentary changes at the level of the RPE were seen after SML but without any visual implications for the patients. Complications like scar

| Treatment | Change in CRT (µm) | Change in BCVA (ETDRS letters) |
|-----------|-------------------|-------------------------------|
| CSC SML   | -131 (range -69.7 to -204)\(^a\) | 6.34 (range -15 to 20)\(^d\) |
| PDT       | -85 (range -76 to -109.8)\(^b\) | 3.87 (range 2 to 8.5)\(^b\)  |
| Observation | -25 (range 26 to -89)\(^c\) | 0.67 (range -2.1 to 2.5)\(^c\) |
| DME SML   | -74.9 (range -138 to 48)\(^e\) | 1.26 (range -6.6 to 19)\(^f\) |
| Conventional laser | -43.6 (range -145 to 28.7)\(^f\) | -0.29 (range -7.3 to 7.5)\(^f\) |
| BRVO SML  | -122.59 (range -272 to -40.5)\(^g\) | 2.98 (range -3.5 to 9.5)\(^g\) |

CSC central serous chorioretinopathy, DME diabetic macular edema, BRVO branch retinal vein occlusion, BCVA best corrected visual acuity, CRT central retinal thickness, ETDRS Early Treatment Diabetic Retinopathy Study Group letters, PDT photodynamic therapy, SML subthreshold micropulse laser

\(^a\) 199 patients from 11 studies, 7 studies excluded from the calculations, one due to prior PDT treatment [37], six due to absence of information about the CRT

\(^b\) 100 patients from 3 studies

\(^c\) 49 patients from 3 studies

\(^d\) 216 patients from 14 studies, two studies excluded due to prior PDT [37, 41], two due to absence of information about the concrete BCVA [28, 31]

\(^e\) 613 patients from 11 studies

\(^f\) 195 patients from 7 studies

\(^g\) 80 patients from 3 studies, one study excluded from the calculation due to prior conventional laser treatment [56]
formation, visible laser burns, or CNV did not occur.

**DIABETIC MACULAR EDEMA (DME)**

DME is a frequent complication of diabetic retinopathy (DR) and the most common cause of visual impairment in patients with DR [5]. Since the ETDRS trial [1, 73] showed that laser photocoagulation reduced the risk of moderate visual loss by 50% in eyes with clinically significant macular edema, laser photocoagulation became the standard therapy for DME for many years. Depending on the kind of edema, the treatment pattern can be selected: a focal photocoagulation for localized areas of leakage and a grid pattern for a diffuse macular edema. Continuous-wave photocoagulation comes with potential side effects like epiretinal fibrosis, CNV, and enlargement of laser scars [7, 8, 74]. Table 3 shows only the prospective studies investigating micropulse laser treatment for diabetic macular edema. A total of 613 patients from 11 studies were included in the calculations. The inclusion and exclusion criteria varied between studies; some did not allow prior treatment at all, most of them only excluded patients with treatment in the prior 3–6 months. All listed studies were included in the calculations for change in CRT and BCVA. Seven studies had a control group consisting of 195 patients treated with conventional laser. The same calculations were performed for those studies.

Table 4 displays the treatment outcome after SML and conventional laser for DME.

**Safety**

In the majority of studies no laser scars occurred after SML. Four studies reported scar formation or pigmentary changes in a small amount of eyes after SML treatment [48, 50, 51, 54]. Retinal changes were only observed in eyes treated with duty cycles of 15%; lower duty cycles did not lead to scar formation in the listed studies. Venkatesh [49] et al. reported focal void regions in multifocal electroretinogram in 4 out of 23 eyes after SML treatment with 10% duty cycle compared to 18 out of 23 eyes after conventional laser.

**MACULAR EDEMA DUE TO RETINAL VEIN OCCLUSION (RVO)**

Macular edema is a common complication of branch RVO (BRVO) [75]. Grid laser photocoagulation reduces the visual acuity loss after BRVO with macular edema [75]. Parodi et al. [59] reported a similar outcome in visual acuity improvement and resolution of macular edema after SML treatment compared to conventional laser, but without retinal changes after SML. Table 3 summarizes studies investigating SML treatment for macular edema after BRVO. In total 80 patients from three studies could be included in the calculations, and one study was excluded because of prior conventional laser treatment [56]. As a result of the small number of studies and the variety in control groups (bevacizumab, SML + triamcinolone, conventional laser), the control groups were not separately analyzed. Only one study [48] had a control group where patients were treated with anti-VEGF agents, the current standard therapy for macular edema due to BRVO.

Table 4 presents the treatment outcome after SML for macular edema after BRVO.

**Safety**

No study described complications like scar formation, visible laser burns, or CNV.

**PROBLEMS AND CHALLENGES OF SML TREATMENT**

Although the majority of the studies showed some efficacy of the SML treatment for CSC, DME, or BRVO, the treatment parameter differed significantly between the individual studies. No study compared the outcome of SML with different treatment parameters like higher or lower duty cycle. Concerning the treatment power, most authors titrated the power individually for each patient, but the
path was not consistent. The titration is probably the most challenging part of the SML treatment. Since the laser surgeon did not see an effect of the treatment, there is a high risk of undertreatment and treatment failure accordingly. A solution to this problem could be to use fixed laser parameters with the same power for all patients. But so far there is not enough published data to choose the best treatment power and to evaluate the safety and the treatment success of subthreshold micropulse treatment with fixed parameters. For the future, controlled trials comparing treatment outcome and safety of individual titrated SML treatment and SML treatment with fixed parameters would be desirable. Those studies should include safety follow-up with multimodal imaging including autofluorescence, OCT, and fundus photographs as well functional follow-up with microperimetry or multifocal electroretinogram.

CONCLUSION

For CSC, the presented studies showed a higher efficacy of the micropulse laser treatment for both morphology and visual function in comparison to no treatment or PDT. The decrease in CRT was highest after SML (−131 μm), followed by PDT (−85 μm) and the no-treatment group (−25 μm). Moreover, 64% of patients showed no SRF after SML compared to 46% after PDT and 8% after observation.

No study reported any complications after up to five SML treatment sessions, so even an early treatment could be considered for potentially better results. Chen et al. [29] showed that the SML treatment outcome was best in patients with source leakage without RPE atrophy. The investigated literature did not allow an evaluation of the best treatment parameter or the best laser wavelength.

Regarding the treatment of DME, the investigated studies showed efficacy also in morphology and function. The decrease in CRT and increase in BCVA after SML (−74.9 μm and +1.26 ETDRS letters) was better than after conventional laser (−43.6 μm and −0.29 ETDRS letters), but no study had a control group in which patients were treated with anti-VEGF agents. After the RISE and RIDE studies [76] and the approval of ranibizumab for the treatment of DME, anti-VEGF agents became the standard treatment for DME. Without any trial, comparing SML treatment with anti-VEGF agents, we do not know when SML treatment could be an alternative first-line treatment for DME. Nevertheless, SML might be an option in patients not responding sufficiently to, or who are not able to follow an anti-VEGF therapy (e.g., high costs, compliance problems due to frequent visits for the injections and ophthalmological controls). Chen et al. [77] had come to a similar result in their meta-analysis of randomized controlled trials comparing subthreshold micropulse diode laser photocoagulation and conventional laser. They reported a significantly better visual acuity and a similar decrease in CRT after SML compared to conventional laser. They underline the advantage of the SML treatment in terms of the affordability compared to the cost-intensive anti-VEGF therapy.

On the subject of macular edema after BRVO, SML treatment shows some efficacy as well. But in comparison to the current standard treatment, intravitreal anti-VEGF, SML was inferior to intravitreal bevacizumab [56]. However, similar to DME, SML treatment could be an option for adjunct treatment for selected patients.

In summary, in all three indications micropulse laser is an efficacious and safe treatment option. Owing to its higher efficacy and the excellent safety profile compared to PDT, it could become the first-line therapy in CSC, potentially even in acute cases.

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Data Availability. The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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