Review

NONDAMAGING RETINAL LASER THERAPY FOR TREATMENT OF CENTRAL SEROUS CHORIORETINOPATHY

What is the Evidence?

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Purpose: To summarize the literature addressing subthreshold or nondamaging retinal laser therapy (NRT) for central serous chorioretinopathy (CSCR) and to discuss results and trends that provoke further investigation.

Methods: Analysis of current literature evaluating NRT with micropulse or continuous wave lasers for CSCR.

Results: Sixteen studies including 398 patients consisted of retrospective case series, prospective nonrandomized interventional case series, and prospective randomized clinical trials. All studies but one evaluated chronic CSCR, and laser parameters varied greatly between studies. Mean central macular thickness decreased, on average, by ~80 μm by 3 months. Mean best-corrected visual acuity increased, on average, by about 9 letters by 3 months, and no study reported a decrease in acuity below presentation. No retinal complications were observed with the various forms of NRT used, but six patients in two studies with micropulse laser experienced pigmentary changes in the retinal pigment epithelium attributed to excessive laser settings.

Conclusion: Based on the current evidence, NRT demonstrates efficacy and safety in 12-month follow-up in patients with chronic and possibly acute CSCR. The NRT would benefit from better standardization of the laser settings and understanding of mechanisms of action, as well as further prospective randomized clinical trials.

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Central serous chorioretinopathy (CSCR) is the fourth most common nonsurgical retinopathy behind age-related macular degeneration, diabetic retinopathy, and branch retinal vein occlusion.[1] It affects roughly 10 men and 2 women per 100,000 people, which are often of working age (peak prevalence at 45 years) with high visual demands.[2]

The pathophysiology of CSCR has been attributed to hyperpermeable choroidal vessels, impaired choroidal vascular autoregulation, and dysfunction of the retinal pigment epithelium (RPE) barrier and pumping.[3] Most treatments, including laser photocoagulation, transpupillary thermotherapy (TTT), and photodynamic therapy, have been aimed at closing down the focal leak, whereas the vascular endothelial growth factor inhibitors have been directed at prevention of fluid accumulation. Common presenting visual symptoms include blurred vision with a relative central scotoma, metamorphopsia, dyschromatopsia,

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micropsia, reduced contrast sensitivity, and hypermetropization.[4,5]

Although no formal diagnostic criteria for CSCR exist, acute CSCR is characterized by serous detachment of the neurosensory retina and/or detachment of the retinal pigmented epithelium associated with monofocal or multifocal points of leakage on fluorescein angiography (FA).[1] These findings are best evaluated with multimodal retinal imaging, including fundus photography, autofluorescence, FA, indocyanine green angiography, and optical coherence tomography (OCT).[6]

A large fraction of acute CSCR resolves spontaneously within 3 months of the symptoms onset. However, up to 20% of patients have persistent subretinal fluid and vision loss lasting beyond 6 months.[7,8] When subretinal fluid persists longer than 3 or 4 months, the term chronic CSCR is generally used.[3,9–11] This is typically characterized by multifocal irregularly distributed RPE changes associated with variable extent of angiographic leakage, chronic subretinal and sub-RPE fluid, leading to permanent visual disturbance.[1] Central serous chorioretinopathy may result in subretinal fibrin accumulation or choroidal neovascularization, which may lead to severe vision loss.[3]

The disease is bilateral in ~30% of cases,[7] recurrences in the same or opposite eye occur in 30% to 50% of cases,[12] and only approximately 5% of all cases result in permanent and marked visual dysfunction.[13] Until now, initial observation in acute cases is considered reasonable because any treatment except for nondamaging retinal laser therapy (NRT) may be associated with retinal tissue damage. Therefore, treatment is currently considered only in cases of chronic and/or recurrent CSCR and is offered depending on the patient's visual demands, presence of modifiable risk factors such as corticosteroids, preferences of the treating physician, and the status of the disease. However, if NRT is proven to be safe and effective, it might become the preferred first line of therapy to improve vision and prevent retinal structural damage associated with chronicity of CSCR.

The combination of transient and permanent signs and symptoms make CSCR a complex disease to diagnose and manage, for which there is still no medication or other treatment specifically approved by the Food and Drug Administration. Treatment options include photodynamic therapy (PDT), various forms of retinal laser photocoagulation, and a host of oral medications with limited clinical evidence and possible side effects including anti-corticosteroids, adrenergic blockers, systemic carbonic anhydrase inhibitors, and aspirin.[14] Anti–vascular endothelial growth factor therapy has been shown to have modest efficacy[15] as well.

Photodynamic therapy with verteporfin damages vascular endothelium in an illuminated area, resulting in reduced choroidal perfusion and narrower choroidal vasculature, thereby decreasing choroidal hyperpermeability, a key factor in CSCR.[16] To date, PDT is the proven treatment in cases with central involvement that require intervention.[17] Photodynamic therapy at full dose of verteporfin,[12] half dose,[18] and half laser fluence[19] have been shown to be efficient in cases of acute, chronic, and recurrent CSCR and may be applied within the parafoveal zone. Although the risks of PDT decrease when decreasing the dose of verteporfin or the laser fluence, it is still possible to induce choroidal ischemia,[20] neuroretinal thinning,[21] and very rarely RPE tears,[22] when large pigment epithelial detachments are treated. Furthermore, injection of the verteporfin makes PDT an invasive intervention with potential systemic complications, such as temporary vision loss, tissue damage from dye extravasation, or skin damage from excessive exposure to sunlight after treatment.

Retinal laser photocoagulation, currently performed with continuous wave 532-nm Nd:YAG laser, and earlier with argon green (514 nm) laser, but also reported with ruby,[23] krypton, and diode (810 nm) lasers,[24] was the historic treatment of choice for CSCR that did not resolve spontaneously, and remains a viable treatment option in cases of focal angiographic leakage outside the parafoveal zone. A prospective case series found that laser photocoagulation resulted in slower resolution of visual acuity and subretinal fluid (SRF) compared with half-dose PDT, but at 3 months and beyond, the anatomical and functional outcomes were identical.[25] When compared with observation, laser photocoagulation leads to more rapid resorption of subretinal fluid and subsequent faster recovery of visual acuity.[26,27] Although laser photocoagulation is effective, this treatment permanently damages retinal tissue at the site of laser application,[28] forming scotoma,[24] and may result in choroidal neovascular membrane (CNVM) at the site of the laser scar, if Bruch membrane was ruptured.[29]

To reduce collateral damage induced by photocoagulation, laser parameters, including power, pulse duration and repetition, have been modified to reduce temperature rise in the retina. This diverse general class of treatments has been often called "subthreshold" laser therapy, which includes the more specific classification into subvisible damaging therapies and nondamaging therapies.

In addition to PDT, an example of ophthalmoscopically subvisible, but damaging, treatment is the selective retinal therapy, in which RPE cells are selectively destroyed by exploding melanosomes with microsecond or nanosecond pulses.[30] Photoreceptors

and Bruch membrane are spared in this treatment. The RPE cells in the surrounding areas then stretch, migrate, and proliferate to refill the damage zone.[31,32] It is assumed that this process improves the cellular tight junctions and pumping functions of RPE cells and clears the Bruch membrane by activation of matrix metalloproteinase enzyme,[33] thereby increasing its permeability.

Transpupillary thermotherapy was first suggested to treat choroidal melanomas and later as a less damaging alternative to photocoagulation in cases of subfoveal leaks. Proponents of this approach have hypothesized a selective damaging effect of heating on actively dividing cells in newly formed blood vessels because of their higher susceptibility to thermal injury than nondividing cells in normal tissue. The estimated retinal temperature elevation with TTT at clinical settings (810 nm, 800 mW, 60 seconds, 3 mm spot size) is approximately 10°C.[34] The mechanism of treatment of choroidal neovascularization by TTT may occur through vascular thrombosis, apoptosis, or the thermal inhibition of angiogenesis.[34] TTT seemed to be safe and moderately effective when compared with PDT and conventional laser photocoagulation for CNVM and CSCR[35]; however, without titration, this procedure occasionally resulted in retinal damage.[36]

A pulsed version of a similar laser with smaller spot size (125 μm) replaced TTT for nondamaging therapy. So-called subthreshold diode (810 nm) micropulse (SDM) laser (Iridex Corp, Mountain View, CA) delivers 100 milliseconds to 300 milliseconds bursts of pulses of 0.1 milliseconds to 0.3 milliseconds in duration at 500 Hz repetition rate (5%–15% duty cycle), with the average power set below detectable tissue damage by adjustment of the pulse duty cycle and peak power. Other lasers capable of "micropulse" therapy include the 532-nm "Integre Duo" laser (Ellex, Adelaide, Australia) and the 577-nm "Supra Scan" laser (Quantel Medical, Clermont-Ferrand, France). As described in this review, "subthreshold" micropulse laser has been shown to be effective in the treatment of CSCR. However, the lack of a well-defined titration procedure and a wide variety of settings in various clinical trials is reflected in the variable results with this technology exhibited herein.

A more recent approach to NRT is based on adjustment of the laser power and pulse duration, which relates the titration settings, producing a barely visible lesion to nondamaging treatment settings.[37] This algorithm, called EndPoint Management (EpM), is based on modeling of the temperature-dependent rate of protein denaturation as an Arrhenius process.[38] The range of tissue response below damage threshold was established by detection of the heat shock protein expression.[37,39,40] The EpM software is available in the recent models of PASCAL laser (Topcon Medical Laser Systems, Santa Clara, CA).

Nondamaging retinal laser therapy is thought to work by heating the chorio-retino-RPE complex above the onset of therapeutic response but below the tissue damage,[37] thereby avoiding the visible burns, tissue necrosis, and related collateral effects.[41] Although the rationale for patient safety is clear, its exact mechanism of action remains to be elucidated. It has been demonstrated that tissue response involves expression of heat shock proteins, including HSP70.[37,40] Heat shock proteins act as chaperones for refolding misfolded proteins, thereby potentially rejuvenating RPE cells and restoring their cellular function.[40] In addition, HSPs inhibit apoptosis and downregulate inflammation. NRT has shown efficacy in the treatment of diabetic macular edema,[32,42–45] macular edema secondary to retinal vein occlusion,[46] age-related macular degeneration,[47–51] and macular telangiectasia.[37]

Retinal laser therapy without tissue damage offers the multiple potential advantages compared with conventional photocoagulation: 1) treatment with high spot density to boost the therapeutic response, 2) capability to treat foveal areas, 3) possibility of retreatment in chronic conditions or with insufficient response to a single treatment, and 4) improved preservation of color vision and contrast sensitivity.[52] Given the emerging interest in NRT and its application in CSCR, the purpose of this review was to compare and integrate the peer-reviewed publications evaluating NRT in CSCR to 1) demystify NRT for clinicians not currently using it; 2) provide a reference for physicians wishing to use NRT by tabulating the various laser types, parameters, and techniques, in addition to treatment outcomes regarding resolution of subretinal fluid, best-corrected visual acuity (BCVA), and central macular thickness (CMT); and 3) evaluate trends within these studies that provoke further investigation.

Methods

A computer-assisted search of English language articles was performed using the PubMed index. Varying combinations of the terms "subthreshold," "nondamaging," "laser," "central serous choroidopathy," "central serous retinopathy," and "central serous chorioretinopathy" were used and cross-checked with references from related articles. As of August 2016, a broad search with these terms resulted in 16 peer-reviewed publications.[9–11,37,53–64] No articles were omitted, all were tabulated according to study design,

chronicity of disease, inclusion and exclusion criteria, and laser settings and analysed quantitatively based on BCVA and OCT results.

For comparison of BCVA, visual acuity data were converted to Early Treatment Diabetic Retinopathy Study (ETDRS) equivalent: when presented in Snellen, using the formula ETDRS = 85 + (50 × log [Snellen fraction]), and when presented in logMAR, using the formula ETDRS = 100 − (50 × logMAR).[65,66] The improvement from baseline was then calculated and plotted over time, as shown in Figure 1. The weighted average was calculated based on the number of patients in each study at each time point and is plotted as the 2-point moving average trend line in Figure 1.

Regarding OCT data, only one study (Yadav et al[9]) recorded subretinal fluid height, whereas the remaining studies assessed the CMT, and therefore, this measure was used to compare anatomical outcomes in this review. Only two studies[11,57] explicitly defined CMT as the distance from the inner retinal surface to the inner border of the RPE, including subretinal fluid, if present. The other studies assumed to follow the same definition. The change in CMT from baseline over time is shown in Figure 2. Similar to the BCVA graph, a weighted average was calculated based on the number of patients in each study at each time point and is plotted in Figure 2 as the 2-point moving average line.

One study[57] followed two groups of patients, one receiving NRT at the onset and one initially observed and then crossed over to NRT at varying time intervals. The initially observed and subsequently crossed over patients were excluded from graphical analysis as the study did not subcategorize outcomes based on the varying crossover time points. Many studies presented "final" BCVA and OCT data, wherein patients had varying duration in the study; in these cases, the final BCVA and OCT CMT was time-designated to be at the average time of duration in the study.

The following studies were excluded from the quantitative data analysis: Scholz et al[63] and Breukink et al[61] included patients previously treated with PDT.

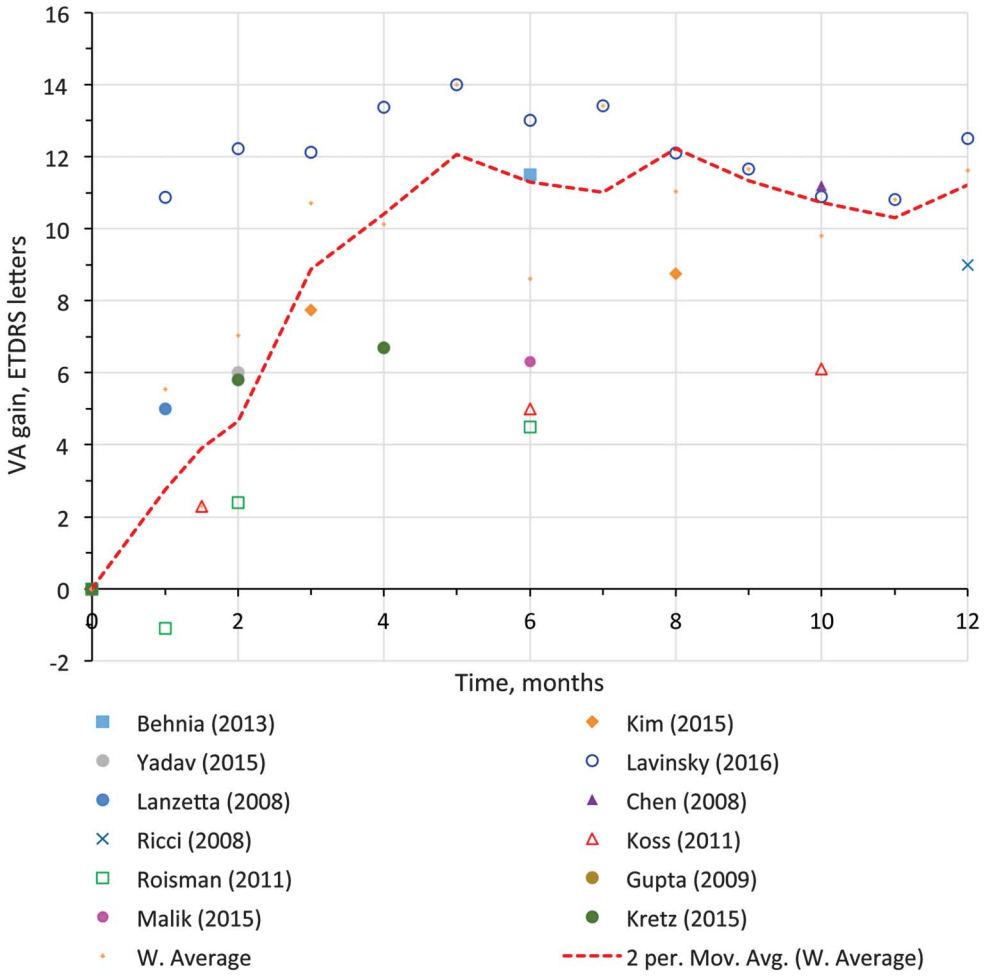

Fig. 1. Increase in visual acuity measured in ETDRS letters compared with baseline. Dash line depicts the two-point moving average of the data, weighted by the number of patients in each study.

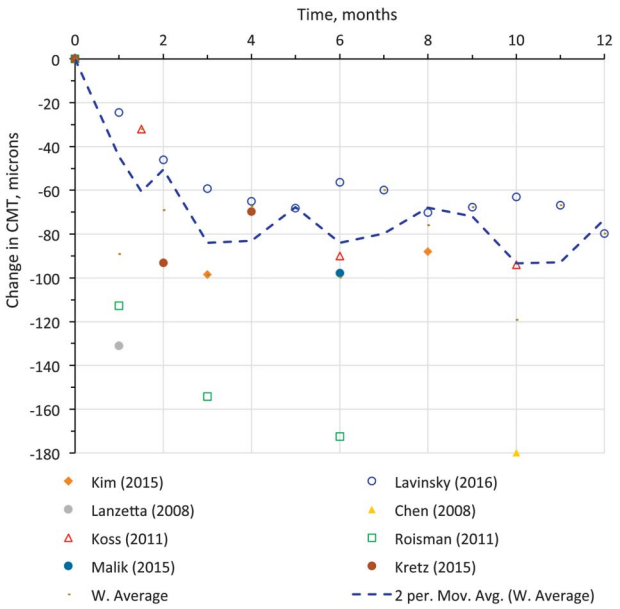

Fig. 2. Decrease in the central macula thickness compared with baseline. Dash line depicts the two-point moving average of the data, weighted by the number of patients in each study.

Although the article by Scholz et al[63] included some treatment-naive patients, they did not provide any separate data on the subgroup without PDT pretreatment. The publication by Elhamid et al[62] reports self-contradictory data. The study by Gupta et al[58] consisted of brief retrospective case reports with highly variable inclusion and exclusion criteria and methodology, and the article by Gawęcki[64] reports a single case of unknown chronicity, which was previously treated with intravitreal bevacizumab (BCZ).

For simplicity, error bars and standard deviations were not included in the graphs, but unless otherwise mentioned, all the reported quantitative results reached statistical significance based on the parameters of each individual study. Statistical analysis between studies was not performed given the wide range in study designs. In addition, the time points at which patients were re-treated were not shown in Figures 1 and 2 because of a wide variability of re-treatment criteria and timing.

Results

As listed in Table 1, 16 publications[9–11,37,53–63] exploring the effect of various forms of nondamaging laser therapy on central serous retinopathy, including 398 patients in total, were found. These studies included retrospective case series (study n = 6, patient n = 1–38), prospective nonrandomized interventional case series (study n = 7, patient n = 7–59), and prospective randomized clinical trials (study n = 3, patient n = 15–62). A wide variety of laser settings in these studies are summarized in Table 2.

In regards to patient safety, no retinal damage or complications (such as laser-induced CNVM or scars) were observed in association with the laser treatments in all the included studies. The laser parameters were selected with the intent of producing no tissue damage. Therefore, this treatment modality is hereafter referred to as "nondamaging retinal laser therapy" (NRT) for the sake of simplicity.

The overwhelming majority of studies (15 of 16) evaluate the response to NRT in chronic CSCR, with only 1 study[53] describing acute conditions, defined as $<$1 month of visual symptoms attributable to CSCR. This group reported a beneficial effect of NRT 6 months after intervention, with 72.2% of patients in the treatment group reaching a BCVA of 20/20 in comparison with 55.6% in the observation group ($P < 0.001$). Despite attempted randomization, it is worth noting that patients in the NRT group had overall worse baseline BCVA than patients in the observation group. Among the studies evaluating chronic CSCR, the definition of "chronic" varied, ranging from visual symptoms attributable to CSCR of $>$6 weeks (n = 1), 3 months (n = 6), 4 months (n = 2), 6 months (n = 3), some combination thereof (n = 1), and not defined (n = 2). One study[59] evaluated NRT on patients with previously untreated CSCR, with the average duration of symptoms of 27.6 months, and an upper limit of 77 months. This group reported a mean BCVA improvement of 6.3 ETDRS letters and a mean decrease in CMT of 97.8 μm. Although both were statistically significant, there was no comparison to observation or alternative intervention.

The remainder of inclusion and exclusion criteria varied widely, with some studies accepting previous steroid use and previous laser therapy (subthreshold or visible), some excluding one or the other, and some not clearly mentioning such criteria. Most studies diagnosed patients with CSCR and subsequently included them in analysis based on a combination of symptomatology, fundus appearance, the presence of subretinal fluid on macular OCT, and the presence of angiographic leakage on FA and/or indocyanine green angiography. However, this was not standardized between studies.

Although most studies reported the effects of NRT on CSCR patients without comparison to observation or alternative intervention, 4 did make prospective treatment comparisons, as described in Table 1. Behnia et al[53] compared NRT to observation in acute CSCR. Koss et al[10] compared NRT to both observation and intravitreal BCZ in chronic CSCR, although patients were allowed to choose their treatment

Table 1. Overview of the Studies

Study Group (Publication Year)	Acute vs. Chronic CSCR	Type of Study	N = Eyes
Behnia et al[53]	Acute (<1 month)	Prospective, randomized, double-blind, clinical trial comparing NRT (n = 18) to observation (n = 19)	37
Kim et al[54]	Chronic (>6 months)	Retrospective, interventional case series	10
Yadav et al[9]	Chronic (>3 months)	Retrospective, interventional case series	15
Lavinsky et al[37]	Chronic (>4 months)	Prospective, nonrandomized, interventional case series	21
Lanzetta et al[55]	Chronic (>3 months)	Prospective, nonrandomized, interventional case series	24
Chen et al[11]	Chronic (>4 months)	Prospective, nonrandomized, interventional case series	26
Ricci et al[56]	Chronic (>6 months)	Prospective, nonrandomized, interventional case series	7
Koss et al[10]	Chronic (>3 months)	Prospective, nonrandomized, interventional case series comparing observation (n = 26) to SDM (n = 16) to intravitreal BCZ injection (n = 10) via patient choice	52
Roisman et al[57]	Chronic (>6 months)	Prospective, randomized, double-blind, sham-controlled pilot trial comparing NRT (n = 10) to sham laser (n = 5) with subsequent treatment crossover of sham group	15
Gupta et al[58]	Acute and chronic	Retrospective brief case reports	5
Malik et al[59]	Chronic (>3 months)	Retrospective, interventional case series	11
Kretz et al[60]	Chronic (>3 months)	Prospective, randomized, double-blind, clinical trial comparing NRT (n = 20) to hdPDT (n = 24) to observation with sham laser (n = 18)	62
Elhamid et al[62]	Chronic (>3 months)	Prospective interventional noncomparative clinical study	15
Scholz et al[63]	Chronic (>6 weeks)	Retrospective case series	38
Breukink et al[61]	Chronic (not defined)	Interventional prospective case series	59
Gawęcki[64]	Chronic (not defined)	Retrospective brief case report	1

modality, perhaps introducing bias. This group found that NRT was superior to both observation and BCZ, resulting in enhanced visual acuity with improvement in 6 ETDRS letters with NRT compared with loss of 1 and 2 letters with BCZ and observation, respectively, at 10 months. Additionally, improvement in microperimety and decrease in angiographic leakage was observed with NRT, with 2.5% persistent leakage in the NRT group compared with 60% and 92% with BCZ and observation, respectively. Roisman et al[57] also compared NRT (SDM) to initial observation followed by subsequent crossover of the observation arm at 3 months to NRT; this was the only study with a crossover design. At 3 months, all patients were evaluated for potential re-treatment (including potential for crossover from sham to NRT) if meeting at least two of three criteria: decreased visual acuity of at least one line from baseline, macular SRF on OCT, and "significant leakage" on FA. At 3 months, all the sham patients were crossed over to treatment (as all met re-treatment criteria), with two of the original sham patients requiring two treatments, whereas only one of the originally treated patients required re-treatment based on the above criteria. Even though all the initial sham patients were crossed over to NRT, they did worse than the patients who received NRT from the beginning, with a 6-month BCVA of 31 ± 8.8 ETDRS letters ($P = 0.225$) in the sham/crossover group, and 50 ± 6.8 ETDRS letters ($P = 0.008$) in the NRT group. Ultimately, vision in the crossed over group improved to 39.2 ± 7.1 ETDRS letters ($P = 0.042$) at 12 months, but this was still less than that achieved by the original NRT group. Potential drawbacks to the study include small sample size (10 in NRT group, 5 in original sham) and the fact that patients in NRT group had statistically shorter duration

Table 2. Laser Settings and Treatment Techniques

Study Group	Laser Device	Laser Parameters
Behnia et al[53]	**532 nm** laser, Integre Duo (Ellex)	**Spot size**: 100 μm; **titration**: CW, 50 milliseconds, starting with 80 mW, power reduced in 20% increments until no burn visualized; **treatment**: power at 20% of titration threshold, other parameters kept the same; **mean# spots per TX**: 48 (each eye)
Kim et al[54]	**Micropulse 577 nm** Supra Scan Laser (Quantel Medical)	**Spot size**: 100 μm; **titration**: power derived from threshold test burn with micropulse laser, 15% duty cycle at 20-millisecond burst duration (250–350 mW); **treatment**: power at 50% of titration threshold, 15% duty cycle, 20-millisecond exposure; **mean# spots per TX**: not listed
Yadav et al[9]	**Micropulse 577 nm** Supra Scan Laser (Quantel Medical)	**Spot size**: 100 μm; **titration**: placed superonasally, CW, 200-millisecond exposures, power titrated to cause mild retinal whitening; **treatment**: power 50% of titration threshold (70–200 mW), micropulse mode at 10% duty cycle (0.2 milliseconds ON, 1.8 milliseconds OFF); **mean# spots per TX**: 264 (72–443)
Lavinsky et al[37]	**577 nm** PASCAL laser (Topcon Medical Laser Systems) with EpM titration protocol	**Spot size**: 200 μm; **titration**: power was first titrated for a barely visible burn with 15-milliseconds pulses, which was defined as 100% pulse energy on EpM scale; power range 90–150 mW, with an average of 126 ± 14 mW; **treatment**: 30% pulse energy on EpM scale, with the spot spacing of 0.25 beam diameter; **mean# spots per TX**: 548
Lanzetta et al[55]	**Micropulse diode 810 nm** laser (Iris Medical Oculight Slx Laser; Iridex Corp, Mountain View, CA)	**Spot size**: 200 μm; **titration**: CW, 200-millisecond exposure with power to achieve mild retinal whitening (1–2 W, mean 1.35 W); **treatment**: duty cycle set to 15%, other parameters same as titration; **mean# spots per TX**: 215 (range 90–400)
Chen et al[11]	**Micropulse diode 810 nm** laser (Iris Medical Oculight Slx Laser)	**Spot size**: 125 μm; **titration**: CW 200-millisecond exposure with power to achieve mild retinal whitening (mean laser power was 535 ± 180 mW); **treatment**: duty cycle 15%, other parameters same as titration; **mean# spots per TX**: mean number of laser bursts 240 ± 114
Ricci et al[56]	**Micropulse diode 810 nm** laser (Iris Medical Oculight Slx Laser)	**Spot size**: 75 μm in air, with Volk PDT lens (1.5 × spot magnification), produced a 112.5-μm spot on the retina; **titration**: "to ensure no visible or latent burn would result;" **treatment**: 500-millisecond bursts, 500 mW power, 10% duty cycle, separated by 500-millisecond pauses, for a total treatment time of 50 seconds; with this spot and the laser power set at 500 mW, each micropulse had 5 kW/cm^2 irradiance and 1 J/cm^2 fluence; **mean# spots per TX**: when close to the fovea, the number of sequential exposures was halved from 50 to 25 (25 seconds of treatment time)
Koss et al[10]	**Micropulse diode 810 nm** laser (Iris Medical Oculight Slx Laser)	**Spot size**: 125 μm (117 μm on the retina); **titration**: CW 200-millisecond exposures, adjusting the power "until a light grayish visible burn was noticed (Pcw);" **treatment**: micropulse at 15% duty cycle, the power was doubled (2 × Pcw) with the same 200-millisecond exposure duration; **mean# spots per TX**: "3 repeated applications were delivered at the leakage site(s);" average of 72 shots (averaged including re-treatments)

(*continued on next page*)

Table 2. (*Continued*)

Study Group	Laser Device	Laser Parameters
Roisman et al[57]	**Micropulse diode 810 nm** laser (Iris Medical Oculight Slx Laser)	**Spot size**: 125 μm; **titration**: CW 300-millisecond exposures, power adjusted to the minimum for a visible burn (range: 250–550 mW, mean power 370 mW); **treatment**: micropulse mode with 15% duty cycle, and the power increased by 1.2 $\times$ threshold (range of power during treatment: 300–660 mW, mean 444 mW); **mean# spots per TX**: 457 (range: 299–674)
Gupta et al[58]	**810 nm infrared diode** laser (Iris OcuLight 810SLx, Iridex, Wales, United Kingdom)	**Spot size**: 125 μm; **titration**: burst duration of 200 milliseconds, duty cycle 15%, power increased until threshold burn developed; power then reduced by 20% increments until no burn visualized; **treatment**: power derived from titration (subvisible), other parameters kept the same; **mean# spots per TX**: "a grid of 5–10 exposures was applied at the area of FA leakage"
Malik et al[59]	**Micropulse diode 810 nm** laser (Iris Medical Oculight Slx Laser)	**Spot size**: not mentioned; **titration**: no test burn used; **treatment**: 5% duty cycle, and 200-millisecond to 300-millisecond burst duration; power range: 750–1,000 mW; **mean# spots per TX**: 327 (85–657)
Kretz et al[60]	**Micropulse diode 810 nm** laser (Iris Medical Oculight Slx Laser)	**Spot size**: 75 μm to 125 μm; **titration**: no test burn used; **treatment**: micropulse at 15% duty cycle, 300-millisecond bursts; average power 1.5 W; **mean# spots per TX**: 101
Elhamid et al[62]	**IQ 577** laser (Iridex Corporation, Mountain View, CA)	**Spot size**: 200 μm; **titration**: 50 mW, CW, increased in 10 mW increments until a "barely visible" burn; **treatment**: in micropulse mode with 10% duty cycle, power $\times$ 3 the titration threshold; burst duration of 200 milliseconds; **mean# spots per TX**: 248 ± 85
Scholz et al[63]	**Subthreshold micropulse 577 nm** Supra Scan Laser (Quantel Medical)	**Spot size**: 160 μm; **titration**: 700 mW, increased power until a "just visible" reaction was seen; **treatment**: power reduced to 50% of titration, burst duration of 200 milliseconds, 5% duty cycle; **mean# spots per TX**: not listed
Breukink et al[61]	**Micropulse diode 810 nm** laser (Iris Medical Oculight Slx Laser)	**Spot size**: 125 μm; **titration**: 1800 mW, reduced by 300 mW increments until "no visible reaction"; **treatment**: at titration level, 200-millisecond exposures, 5% duty cycle; **mean# spots per TX**: not listed
Gawęcki[64]	**"577 Yellow multispot laser"**	**Spot size**: 160 μm; **titration**: "titration on the edge of edematous and normal retina"; **treatment**: reduced titration power by half (550 mW), 200-millisecond duration, 5% duty cycle; **mean# spots per TX**: 600

CW, continuous wave.

of symptoms (13.3 ± 7.7 months) versus the original sham group (31.8 ± 24.3 months), perhaps skewing the results in favor of the NRT group. Finally, Kretz et al[60] had the largest number of eyes of all the included studies (n = 62), and in a randomized, prospective manner compared NRT to both observation and half-dose PDT (hdPDT) in chronic (>3 months) CSCR. This study found that both treatment groups (60% NRT vs. 66.7% hdPDT) showed significant improvement in reduction of leakage compared with the control group (37.5%) at 16 weeks. Central macular thickness decreased by 70 μm (NRT), 110 μm (hdPDT), and 89 μm (control). The BCVA in ETDRS letters improved by (+) 6.7 (NRT), +8.5 (hdPDT), and (+) 1.5 (control). No adverse events were attributed to either NRT or PDT. Overall, they concluded that both NRT and hdPDT exhibited efficacy in chronic CSCR, with the hypothesis that efficacy of hdPDT may be greater in more chronic cases, but it is more invasive.

An increase in CMT was reported in one case,[64] where it transiently increased after a second treatment with SDM, followed by ultimate resolution and return of BCVA to pretreatment level with topical bromfenac and intravitreal BCZ.

Perhaps representing the source of most confusion with retinal laser therapy in general, and with NRT in particular, is that the laser type and settings are not standardized and vary greatly between the studies, as listed in Table 2. Behnia et al[53] used 532 nm laser

with power reduced to 20% of the titration threshold. Lavinsky et al[37] used the 577-nm PASCAL laser with EpM software, where pulse duration and power are adjusted to reach 30% of the titration energy. Most variation in settings can be seen with a micropulse laser. With 577 nm laser, Elhamid et al[62] used 10% duty cycle and power tripled compared with the titration burn produced with continuous wave laser. Others used power at 50% of titration level, with duty cycle of 15% (Kim et al[54]), 10% (Yadav et al[9]), and 5% (Scholz et al[63]). The remainder of the studies herein (aside from the study by Gawęcki,[64] where the make and model of the laser was not discussed) used the 810-nm micropulse diode laser, with varying parameters, titration protocols, and number of laser spots, as listed in Table 2. Most studies used a targeted approach, treating the "area of active leakage," "RPE decompensation," and/or subretinal fluid as predetermined on imaging, such as FA, fundus autofluorescence, and/or OCT. Ricci et al[56] adopted the most targeted approach of the studies, using indocyanine green angiography for precise targeting the active leakage spots. Lavinsky et al[37] applied treatment not only to the areas of active leakage but also to adjacent retina encompassing most of the macula.

As shown in Figure 1, all the included studies demonstrated a mean gain in visual acuity. Lavinsky et al[37] demonstrated the largest and the fastest gain in vision, ranging from 11 to 14 letters, starting after 1 month and remaining in that range for the rest of the 12-month follow-up period. As shown in Figure 2, mean CMT decreased in all included studies analyzing NRT, on average by $\sim$80 μm by 3 months. All studies in Figure 2 represent chronic CSCR.

The re-treatment considerations with NRT remain highly debated.[9–11,37,53–60] The indication for re-treatment and the number of eyes received re-treatments with NRT are listed in Table 3. Overall, the number of eyes requiring more than one treatment based on various criteria ranged from 9%[59] to 80%.[60] Many studies[10,11,37,54,55] (n = 5) clustered around 42% to 84% of eyes requiring more than 1 NRT treatment, whereas 4 groups[9,53,56,61] did not include re-treatment in their study design, and 2 groups[58,63] had poorly defined re-treatment criteria.

No study reported any "complications" attributed to treatment, such as visible laser burns, CNVM, or retinal scars. The majority of studies report no visible changes on any of the imaging modalities. Two studies using SDM[55,64] report some pigmentary changes in the RPE attributed to micropulse laser treatment in six patients, although there were no visual consequence to this damage.

Discussion

Review of the published studies about NRT confirmed its efficacy in the treatment of CSCR, as evidenced by improvement in visual acuity and retinal thickness during the 12-month follow-up. Although the visual acuity results are variable between the studies, overall, improvement was achieved during the initial 3 months and maintained afterward in all included studies, as shown in Figure 1. Likewise, mean CMT decreased in all included studies, as exhibited in Figure 2. The average CMT reduction stabilizes around 80 μm after 3 months. However, because very few studies included an observation arm, it is not clear how much these responses are superior to observation. For the cases[10,53,57,60] that did include observation, there was a statistically significant treatment effect noted at all time points.

The question of efficacy begets the issue of "dose," which has never been properly defined in retinal laser therapy. What wavelength, power, duration, spot size, and number of spots should be used to achieve a maximum response? The "micropulse" laser is rather common in clinical practice worldwide, and physicians using this type of modulation of laser power refer to the treatment as "subthreshold micropulse." Some physicians use one dose for all,[43,44] and some apply various strategies of range finding based on a minimally visible lesion, which is defined as "threshold." Then the duty cycle and sometimes the power are reduced to lower the applied energy "below threshold." However, the exact technique is not standardized nor widely agreed upon, and the relation between variations in treatment protocol and patient response is unknown. It is clear though that if laser settings are too low, the treatment will be subtherapeutic, whereas if the settings are too high, there is a danger of damage to RPE or the neural retina, concerning especially when treating near the fovea.

EndPoint Management (EpM) protocol was developed to properly define the therapeutic window, titration procedure, and to standardize NRT. In EpM algorithm, laser power is first titrated to the barely visible lesion using pulses of 15 milliseconds or 20 milliseconds, and this energy is defined as 100%. In animal experiments, it has been established that no tissue damage could be detected below 30% energy on EpM scale,[39] but heat shock protein expression begins above 20%.[37] Therefore, for clinical applications of NRT, the laser is set to 30% on EpM scale. For efficient therapy, laser spots are placed very densely: separated by 0.25 spot diameter, and the treatment

Table 3. Re-treatment Criteria and Applications

Study Group	Re-treatment Criteria	Eyes Receiving NRT Re-treatment (TX)	No. Treatments
Behnia et al[53]	Not tested	Not tested	1
Kim et al[54]	Lack of complete resolution of subretinal fluid by 1 month or "recurrence," that is, reaccumulation of subretinal fluid after previous complete resolution	5 eyes (50%)	1.9 (1–4)
Yadav et al[9]	Not tested	Not tested	1
Lavinsky et al[37]	Laser treatment could be repeated up to every 3 months if subretinal fluid persisted	13 eyes (58%) required 2 TX, 3 eyes (16%) required 3 TX, 2 eyes (10%) required 4 treatments; overall, 84% of eyes required more than 1 TX	2.2 (1–4)
Lanzetta et al[55]	Not clearly defined	3 eyes (12.5%) required 2 TX, 6 eyes (25%) required 3 TX, 1 eye (4%) required 5 TX; overall, 42% of eyes required >1 TX	(1–5)
Chen et al[11]	If incomplete resolution of subretinal fluid 2 months after treatment and/or recurrence thereafter, repeat SDM was performed 2–3 months later	Group 1, no re-TX required in 6 of 6 (0%); Group 2, 6 of 9 eyes (67%) required 2–3 TX; Group 3, 8 of 11 (73%) required 2–3 TX; overall, 14 of 26 eyes (54%) required >1 TX	(1–3)
Ricci et al[56]	Not tested	Not tested	1
Koss et al[10]	Persistent, equal, or increased leakage determined by FA with the presence of equal or more subretinal fluid compared with baseline	NRT eyes: 6 of 16 eyes (38%) required 2 TX, 1 of 16 (6%) required 3 TX; overall, 7 of 16 eyes (44%) required >1 TX; BCZ eyes: 5 of 10 eyes (50%) re-treated with BCZ	1.4 (1–3)
Roisman et al[57]	**Indication**: Not clearly defined; **crossover indication**: decreased BCVA of at least one line from baseline, macular subretinal fluid on OCT, significant leakage on angiography	Original NRT eyes: 1 of 10 eyes (10%) required 2 TX; overall, 1 of 10 (10%) required >1 TX; Sham crossover: ultimately, 2 of 5 eyes (40%) required >1 TX after initial TX when crossing over	**Original TX** 1.1 (1–2), **crossover** 1.4 (1–2), **overall** 1.2 (1–2)
Gupta et al[58]	Variable, no defined criteria	Variable, not defined	Variable
Malik et al[59]	"Clinically significant subretinal fluid persisting after 3 months"	1 of 11 eyes (9%)	1.1 (1–2)
Kretz et al[60]	Persistent, equal, or increased leakage with equal or greater subretinal fluid compared with baseline could be TX with either repeat SDM or repeat PDT	NRT eyes: 14 of 20 (70%) in SDM group got 2 TX, 2 of 20 (10%) got 3 TX; overall, 16 of 20 (80%) received >1 TX; PDT eyes: 6 of 20 (30%) in PDT group got 2 TX	1.8 (1–3)
Elhamid et al[62]	Persistent leakage after 3 months	4 eyes (26%)	1.26 (1–2)
Scholz et al[63]	Not clearly defined	15 eyes required 2 TX (39%), 6 eyes required 3 TX (16%); overall, 55% eyes required >1 TX	1.7 (1–3)
Breukink et al[61]	Not tested	Not tested	
Gawęcki[64]	Not clearly defined	1 eye (the only eye) underwent 2 TX	2 (2)

typically includes ~500 spots. This algorithm is available on newer versions of the PASCAL laser (Slimline and Synthesis, Topcon, Santa Clara, CA).

With the goal of causing no retinal or choroidal damage, NRT offers the following advantages: 1) ability to treat with large number of spots to boost the therapeutic response, 2) the capability to treat foveal areas, 3) possibility of retreatment in chronic conditions or with insufficient response to a single treatment, and 4) improved preservation of color vision

and contrast sensitivity[52] compared with conventional photocoagulation.

Because the laser energy of visible wavelengths is absorbed primarily in RPE, we hypothesize that the maximum beneficial response to NRT is achieved when RPE cells are still viable rather than atrophic. This is supported by the study design of Chen et al[11]—the only group to subcategorize patients based on their presenting phenotype. In this study, patients with chronic CSCR (>4 months) were divided into 3 groups based on fluorescein angiographic patterns: 1) source juxtafoveal leakage without RPE atrophy, 2) source juxtafoveal leakage with RPE atrophy, and 3) diffuse RPE decompensation with indeterminate source juxtafoveal leakage. They reported a trend of increased resorption and decreased recurrence of subretinal fluid along with decreased need for re-treatment in response to NRT in patients with limited RPE atrophy and more focal leakage. No patients in Group 1 (0 of 6) required re-treatment, whereas 73% (8 of 11) of Group 3 patients required 2 to 3 treatments of NRT. This phenotype subcategorization brings up the issue that "RPE decompensation" is not consistently objectively defined across various studies. This general lack of uniformity in treatment indication may affect inclusion criteria, standardization, and subsequent results of the treatment.

Another issue that may affect patient outcomes with NRT is the duration of the disease, whereby chronicity may act as a surrogate of RPE atrophy. Malik et al[59] treated some of the most chronic patients of the groups herein, with an average duration of observed symptoms of 27.6 months and an upper limit of 77 months. As shown in Figures 1 and 2, this group exhibited smaller BCVA improvement and CMT reduction compared with many other groups, although this comparison was not tested for statistical significance.

The safety of NRT as assessed in this review seems to be excellent. Except for 6 patients in 2 studies using SDM,[55,64] which reported some pigmentary changes on RPE attributed to excessive micropulse laser treatment, but without visual consequences, no visible marks of laser treatment have been observed in the remaining 392 patients of 16 studies. One case report[64] describes a reversible decrease in BCVA and increase in CMT in patient with chronic CSCR who already received intravitreal BCZ and one previous treatment of NRT.

The long-term efficacy of NRT for various macular disorders, including CSCR, is currently under investigation in several randomized prospective clinical trials, and better estimation of its longevity will be clarified with longer follow-up.

Conclusions

Based on the current clinical evidence presented herein, NRT is safe and effective in short-term follow-up in patients with chronic and possibly acute CSCR. Because of wide variations in study design and laser protocol, limited direct comparisons can be made between the groups and with untreated controls. The NRT would benefit from better standardization of the laser settings, especially among physicians using "micropulse" lasers. In addition, although promising associations have been established for cellular response to NRT, better understanding of the mechanisms of action leading to clinical benefits would help in further optimization of the laser therapy for macular diseases. Even more importantly, prospective, randomized and controlled studies should be performed to better assess its efficacy in chronic and acute CSCR and other macular disorders. Effective NRT can serve not only as adjunct or alternative to PDT for chronic cases, but it may become the preferred first line of therapy in CSCR to improve vision and prevent retinal structural damage associated with chronicity of the disease.

Key words: central serous chorioretinopathy, central serous choroidopathy, central serous retinopathy, laser, nondamaging, retinal laser therapy, subthreshold.

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