SUBTHRESHOLD MICROPULSE YELLOW LASER VERSUS SUBTHRESHOLD MICROPULSE INFRARED LASER IN CENTER-INVOLVING DIABETIC MACULAR EDEMA

Morphologic and Functional Safety

STELA VUJOSEVIC, MD, PHD,* FERDINANDO MARTINI, MD,* EVELYN LONGHIN, DSC,† ENRICA CONVENTO, DSC,* FABIANO CAVARZERAN, MSC,* EDOARDO MIDENA, MD, PHD*†

Background: To evaluate and compare in vivo retinal and choroidal morphologic changes and macular function in patients treated with yellow (Y-MPL) or infrared (IR-MPL) subthreshold micropulse laser in center-involving diabetic macular edema.

Methods: Prospective, randomized, single institution, comparative 6-month pilot study of 53 eyes (53 patients with diabetes). Inclusion criteria were previously untreated center-involving diabetic macular edema with central retinal thickness ≤400 μm (mild diabetic macular edema). Y-MPL or IR-MPL treatment was performed in a standardized pattern, using in both cases the lowest duty cycle (5%). Morphologic outcomes were the visibility of laser spots (on color fundus photographs [COL], fundus autofluorescence, fluorescein angiography, and spectral domain optical coherence tomography), retinal thickness and volume changes, foveal choroidal thickness changes, and integrity and reflectivity of the outer retinal layers. Visual function outcomes were variation in mean 4° and 12° retinal sensitivity and best-corrected visual acuity.

Results: Twenty-six eyes were treated with Y-MPL and 27 eyes with IR-MPL. No visible laser spots on the retina were found on COL, fundus autofluorescence, and fluorescein angiography in both treatment groups at 3 months and 6 months of follow-up. Central retinal thickness, macular volume, foveal choroidal thickness, and best-corrected visual acuity were not significantly different at any follow-up visit between the two treatment groups. There were no changes in the integrity of the external limiting membrane or inner segment/outer segment junction in both treatment groups. Mean central 4° retinal sensitivity increased in both treatment groups at 6 months ($P = 0.01$ and $P = 0.04$, respectively). Mean central 12° retinal sensitivity increased in the Y-MPL group only ($P = 0.047$). But, there was no significant difference in mean 4° and 12° retinal sensitivity between the 2 treatment groups at any follow-up visit.

Conclusion: No clinically visible or invisible scars in the macula were found after Y-MPL or IR-MPL treatment. Both Y-MPL and IR-MPL with the lowest duty cycle (5%) and fixed power parameters seem to be safe from the morphologic and visual function points of view in mild center-involving diabetic macular edema.

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Subthreshold micropulse laser at 810 nm (infrared [IR-MPL]) has been recently proposed as a laser treatment option versus the modified Early Treatment Diabetic Retinopathy Study (ETDRS) laser photocoagulation, which is still considered the "gold standard" laser treatment in patients with diabetic macular edema (DME).[1–7]

IR-MPL showed no visible signs of retinal damage on color fundus photograph, optical coherence tomography (OCT), fundus autofluorescence (FAF) and fluorescein angiography (FA), and increased retinal sensitivity compared with the modified ETDRS laser photocoagulation.[6] This is because that

micropulse subthreshold laser treatment probably induces the stimulation of viable retinal pigment epithelium (RPE) cells avoiding any clinically visible damage to the inner or outer retina.[8] In fact, subthreshold micropulse laser spares the neurosensory retina and is selectively absorbed by the RPE. Subthreshold micropulse laser using low duty cycle (the frequency of the train of micropulses) and long "off time" between pulses (low repetition rate) produces and maintains over time subthreshold retinal change without evidence of retinal laser lesions, when compared with the modified ETDRS laser, which delivers energy in a continuous suprathreshold way.[9] Moreover, IR-MPL treatment showed a stabilization or improvement in macular sensitivity versus a significant decrease in macular sensitivity after modified ETDRS laser treatment in patients with DME.[6]

The subthreshold micropulse laser technique is now available also at 577 nm (yellow MPL). But, no data are available about retinal safety when using subthreshold micropulse yellow laser in DME compared with IR-MPL.

The aim of this study was to evaluate and compare morphologic and visual function safety parameters of subthreshold micropulse yellow laser (Y-MPL) versus subthreshold micropulse infrared diode laser (IR-MPL) in eyes with center-involving DME.

Materials and Methods

Patients

A prospective, masked, randomized, pilot study of 53 eyes (53 patients) with untreated center-involving DME was performed. A written consent form was obtained from all patients, as well as the approval from our institutional ethics committee. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

The inclusion criteria were men or women with Type 1 or 2 diabetes mellitus (DM) and an HbA1C $\leq$ 10%, previously untreated center-involving macular edema with central retinal thickness up to 400 μm (mild center-involving DME) confirmed with spectral domain OCT, best-corrected visual acuity (BCVA) of at least 35 letters on the modified ETDRS chart (logMAR 1.0, Snellen 20/200).

From the *Department of Ophthalmology, University of Padova, Padova, Italy; and †Fondazione G. B. Bietti, IRCCS, Roma, Italy.

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Reprint requests: Stela Vujosevic, MD, PhD, Department of Ophthalmology, University of Padova, Via Giustiniani 2, Padova 35128, Italy; e-mail: stela.vujosevic@unipd.it

The exclusion criteria were any type of previous macular treatment (macular laser photocoagulation, vitrectomy, intravitreal steroids, and/or antiangiogenic drugs), any intraocular surgery at least 6 months before the treatment, ischemic or tractional maculopathy, and significant media opacities that precluded fundus examination or imaging.

All patients underwent BCVA determination, slit-lamp biomicroscopy, FAF, FA, spectral domain OCT, and microperimetry (macular sensitivity) before and after treatment. Patients randomly underwent subthreshold Y-MPL or IR-MPL treatment. In case of DME in both eyes, just one eye (that met inclusion criteria) was randomly selected for the treatment. Best-corrected visual acuity, OCT, microperimetry, and FAF were performed at baseline and at 3 months and 6 months of follow-up examination. Fluorescein angiography was performed at baseline and at 6 months.

Imaging

Spectral domain optical coherence tomography. Optical coherence tomography scanning was performed on the spectral domain Cirrus HD-OCT (Cirrus, software version 5.1.1.6; Zeiss Meditec, Dublin, CA). The scanning protocol used for this study was "macular cube 512 $\times$ 128" scan pattern, where a 6 mm $\times$ 6 mm area on the retina is scanned with 128 horizontal B-scan lines, each consisting of 512 A-scans per line. All eyes also underwent line scans centered onto the fovea at 0°, 45°, 90°, and 135° (high-definition scan pattern "HD 5-line raster" consisting of 4,096 A-scans, 6 mm in length).

Retinal thickness was automatically calculated in the 9 ETDRS areas (consisting in a central circular zone with a 1-mm diameter, representing the foveal area, and inner and outer rings of 3 and 6 mm diameter, respectively). The inner and the outer rings are divided into four quadrants: superior, nasal, inferior, and temporal. The average retinal thickness in each of the nine ETDRS subfields was recorded to assess regional changes in retinal thickness after Y-MPL and IR-MPL treatments. In addition, total macular volume (in cubic millimeters) was evaluated. Choroidal thickness in the fovea was manually determined before and after treatment. Subfoveal choroidal thickness was measured as perpendicular distance from the posterior edge of the RPE to the choroid/sclera junction using the linear measure Cirrus tool.[10]

High-definition line scans were evaluated for the integrity and reflectivity of the outer retinal layers (external limiting membrane and inner segment/outer segment junction) and for foveal choroidal thickness.

Fundus autofluorescence. Fundus autofluorescence was recorded with a confocal scanning laser ophthalmoscope (Heidelberg Retinal Angiograph, HRA 2; Heidelberg Engineering, Heidelberg, Germany) using the argon blue wavelength (488 nm). The optical and technical principles of the HRA have been previously described in detail.[11,12] To amplify the autofluorescence signal of the final image, 10 acquired images were aligned and a mean one was calculated from these after detection and correction of eye movements were performed by image analysis software. Digital images were saved on hard disk for further analysis and processing. Fundus autofluorescence images were evaluated for different patterns (normal, increased, and decreased) before and after treatment.[6]

Stereo fundus photography and fluorescein angiography. Color stereoscopic fundus photographs and FA of ETDRS Field 2 were taken in all patients after an adequate dilatation by a certified photographer using the same TOPCON TRC 50IA 35° fundus camera (Topcon, Tokyo, Japan) and saved in JPEG format.[13] Two retinal specialists independently evaluated each pair of images on a 17-inch monitor dedicated for diabetic retinopathy screening. Color photographs were evaluated for the presence of laser scars. Fluorescein angiography images were evaluated for capillary loss and the presence of laser scars at 6 months of follow-up.

Functional Evaluation

Visual acuity. Best-corrected distance visual acuity (BCVA) for each eye was measured by a certified tester using standard ETDRS protocol at 4 m distance with a modified ETDRS distance chart transilluminated with a chart illuminator (Precision Vision, Bloomington, IL).[14] Visual acuity was scored as the total number of letters read correctly (ETDRS score) and expressed both in logMAR (for statistical analysis) and in Snellen ratios.

Microperimetry. Microperimetry was performed on all subjects using the MP1 microperimeter (Nidek, Gamagori, Japan). This instrument has been previously described in detail.[15] For the purpose of this study, the following parameters were used: a fixation target consisting of red ring, 1° in diameter; white monochromatic background at 4 asb; stimulus size Goldman III, with 200 ms projection time; and customized radial grid of 45 stimuli covering central 12° (centered onto the fovea), 1° apart (inner stimuli) and 2° apart (outer stimuli). The starting stimulus light attenuation was set at 10 dB. A 4 to 2 double staircase strategy was used with an automatic eye tracker that compensates for eye movements. Pretest training was performed, and 5-minute mesopic visual adaptation was allowed before starting the test. All subjects underwent microperimetry with dilated pupils. Mean retinal sensitivity was evaluated within central 4° and 12°, approximately covering 1 mm and 3 mm central retina area on OCT map.[16]

Treatment Protocols

Macular laser treatment was performed after pupillary dilation and topical anesthesia according to the randomization assignment. The lens used for the treatment was the Mainster Focal/Grid (Ocular Instruments, Bellevue, WA), with magnification of 1.05 times. Subthreshold Y-MPL treatment protocol was performed with a 577-nm yellow light (Iridex IQ 577; Laser System Iridex Corp, CA) with the following parameters: 100 μm spot size on slit lamp (105 μm spot size on the retina), 5% duty cycle of 0.2 seconds, 250 mW power, and number of spots varying according to the extension of DME. IR-MPL treatment was performed with a 810-nm diode laser (Iridex OcuLight SLx; Iridex Corp, CA) with the following parameters: 125 μm spot size on slit lamp (131 μm spot size on the retina), 5% duty cycle of 0.2 seconds, 750 mW power, and number of spots varying according to the extension of DME. Spots were delivered in a multiple and fully continuous fashion (high-density treatment) up to the edge of the foveal avascular zone.

If needed, retreatment was performed according to the same protocol. Three months after any laser session, retreatment was considered if central subfield OCT macular thickness is $\geq$300 μm, reduction of a subfield OCT macular thickening to $<$50% from baseline, BCVA decrease $>$5 letters on the ETDRS charts.

Statistics

The following parameters were considered as response variables in the study: visual acuity (logMAR), macular sensitivity (dB) (4 and 12 central degrees), macular thickness (in micrometers) (mean thickness of 1-mm central area and mean thickness in the superior, nasal, inferior, and temporal quadrants of the inner and outer macular rings), and volume (in cubic millimeters). For each parameter, changes after treatment were expressed either in absolute values (value at 3 or 6 months after treatment minus pretreatment value) or in percentage values (absolute change over pretreatment value by 100).

To summarize the study parameters, we used the usual methods of descriptive statistics: mean value, standard deviation, and range for normally distributed quantitative variables; median, 25th (Q1), and 75th (Q3) percentiles for asymmetrically distributed

quantitative variables; and frequency and percentages for qualitative variables. Treatment groups were compared at baseline using the Wilcoxon rank-sum test. Changes in response variables at 3 months and 6 months after treatment were evaluated within each laser group and between groups. Two-tailed Wilcoxon signed-rank test with significant level alpha = 0.05 was used. SAS software version 9.1.3 (SAS, Cary, NC) was used for all analyses.

Results

Demographic Data and Baseline Characteristics of the Patients

Of 53 eyes included in this study (53 patients), 26 eyes underwent Y-MPL treatment and 27 eyes IR-MPL treatment. Forty-three patients had Type 2 DM, and 10 patients had Type 1 DM. There were 42 men and 11 women. The mean age of the patients was 63.9 ± 9.2 years with Type 2 DM and 56.3 ± 13.9 years with Type 1 DM. The mean duration of Type 2 DM was 12.8 ± 8.6 years, with mean HbA1C of 7.7 ± 1.4%. The mean duration of Type 1 DM was 25.6 ± 8.1 years, with mean HbA1C of 8.2 ± 0.5%. Before treatment, demographic and macular parameters were not significantly different between the 2 treatment groups (Table 1).

Morphologic Outcomes

Spectral domain optical coherence tomography changes. Both absolute and relative changes in retinal thickness in each macular quadrant at 3 months and 6 months in Y-MPL and IR-MPL treatment groups were evaluated. Briefly, mean central retinal thickness at baseline was 357.8 ± 46.1 μm in the Y-MPL group and 340.1 ± 35.7 μm in the IR-MPL group ($P = 0.17$). At 6-month follow-up, mean central retinal thickness was 339.9 ± 55.7 μm in the Y-MPL group and 335.3 ± 54.5 μm in the IR-MPL group ($P = 0.009$ and $P = 0.45$, respectively vs. baseline values). Central retinal thickness was not significantly different at any follow-up visit between the 2 treatment groups (Wilcoxon sum-rank test, $P = 0.3$ and $P = 0.16$ at 3 and 6 months, respectively). When evaluating mean single subfield retinal thickness, a statistically significant decrease was found in the outer temporal quadrant ($P = 0.02$) and the inner temporal quadrant ($P = 0.05$) at 6 months in the Y-MPL group. A significant decrease in the inner superior quadrant ($P = 0.02$) was found at 6 months in the IR-MPL group. There was no significant absolute or relative thickness change in any quadrant at 6-month follow-up visit between the 2 treatment groups.

At baseline, total macular volume was 11.5 ± 1.3 mm^3 in the Y-MPL group and 11.3 ± 1.0 mm^3 in the

Table 1. Descriptive Statistics

Variable	Y-MPL (N = 26)	IR-MPL (N = 27)
Sex,* N	24:2	18:9
Age,† years	61.7 ± 9.3	63.3 ± 11.7
Diabetes Type 1		
N	7	3
Duration,† years	27.1 ± 9.4	22.0 ± 1.7
HbA1c,† mmol	8.0 ± 0.3	8.7 ± 0.6
Diabetes Type 2		
N	19	24
Duration,† years	12.6 ± 8.3	12.9 ± 9.0
HbA1c,† mmol	7.7 ± 1.0	7.7 ± 1.7

	Y-MPL (N = 26)			IR-MPL (N = 27)		
Variable	Baseline	3 months	6 months	Baseline	3 months	6 months
BCVA						
ETDRS score‡	79.7 ± 6.1	79.4 ± 7.6	78.7 ± 7.4	78.6 ± 7.5	79.3 ± 6.8	77.3 ± 8.2
(Snellen)	(20/25)	(20/25)	(20/25)	(20/25)	(20/25)	(20/32)
Absolute change§		–0.3 ± 4.1	–1.0 ± 4.7		–0.1 ± 2.9	–1.3 ± 4.6
Snellen, N eyes, %						
20/25–20/20	15 (57.7%)	17 (65.4%)	16 (61.5%)	17 (63.0%)	15 (55.5%)	14 (51.8%)
20/50–20/32	9 (34.6%)	7 (26.9%)	10 (38.5%)	10 (37.0%)	11 (40.7%)	12 (44.4%)
20/80–20/63	2 (7.7%)	2 (7.7%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)

*M:F ratio.
†Mean ± standard deviation.
‡Mean number of letters read at 4 m (ETDRS score) ± standard deviation.
§Change in number of letters.
Y-MPL—yellow subthreshold micropulse laser; IR-MPL-infrared subthreshold micropulse laser.

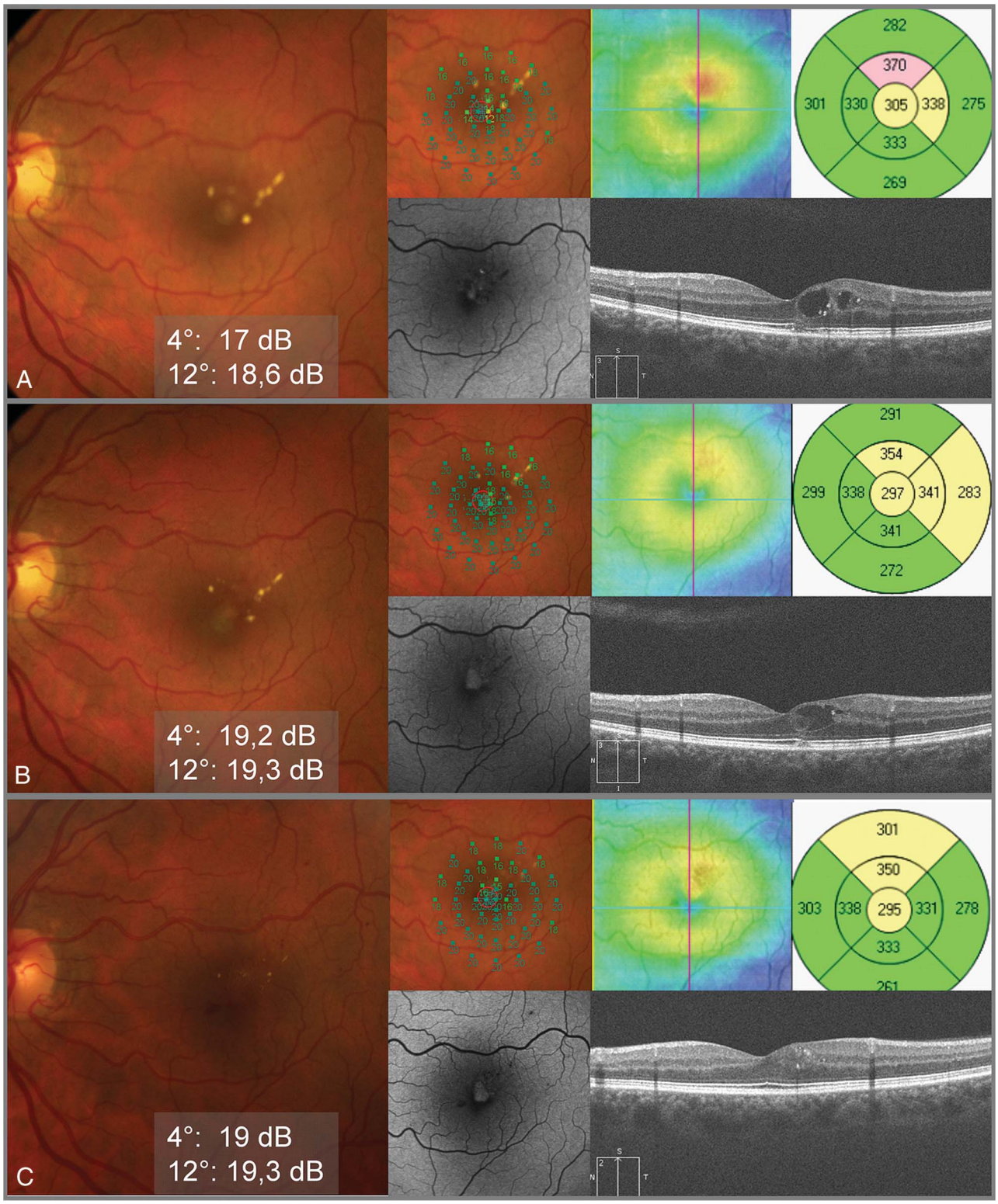

Fig. 1. Baseline (**A**), 3 months (**B**), and 6 months (**C**) of follow-up of a patient with center-involving exudative DME treated twice with subthreshold micropulse yellow laser (Y-MPL). **A.** Top left, color fundus photograph before Y-MPL treatment. Top middle, retina sensitivity map covering central 12° obtained by microperimetry. Bottom middle, FAF. Top right, OCT retinal thickness map and SD-OCT high-definition linear scan before Y-MPDL treatment. **B** and **C.** Follow-up of the same patient at 3 months (**B**) and 6 months (**C**) after treatment. Color fundus photograph and FAF image after Y-MPL treatment showing no retinal or RPE signs of laser treatment. Hard exudates progressively decreased over time. Microperimetry shows increased mean retinal sensitivity, both within the central 4°and 12°areas. Optical coherence tomography retinal thickness map shows decreased retinal thickness. No outer retinal layer changes can be seen after laser on spectral domain OCT linear scan.

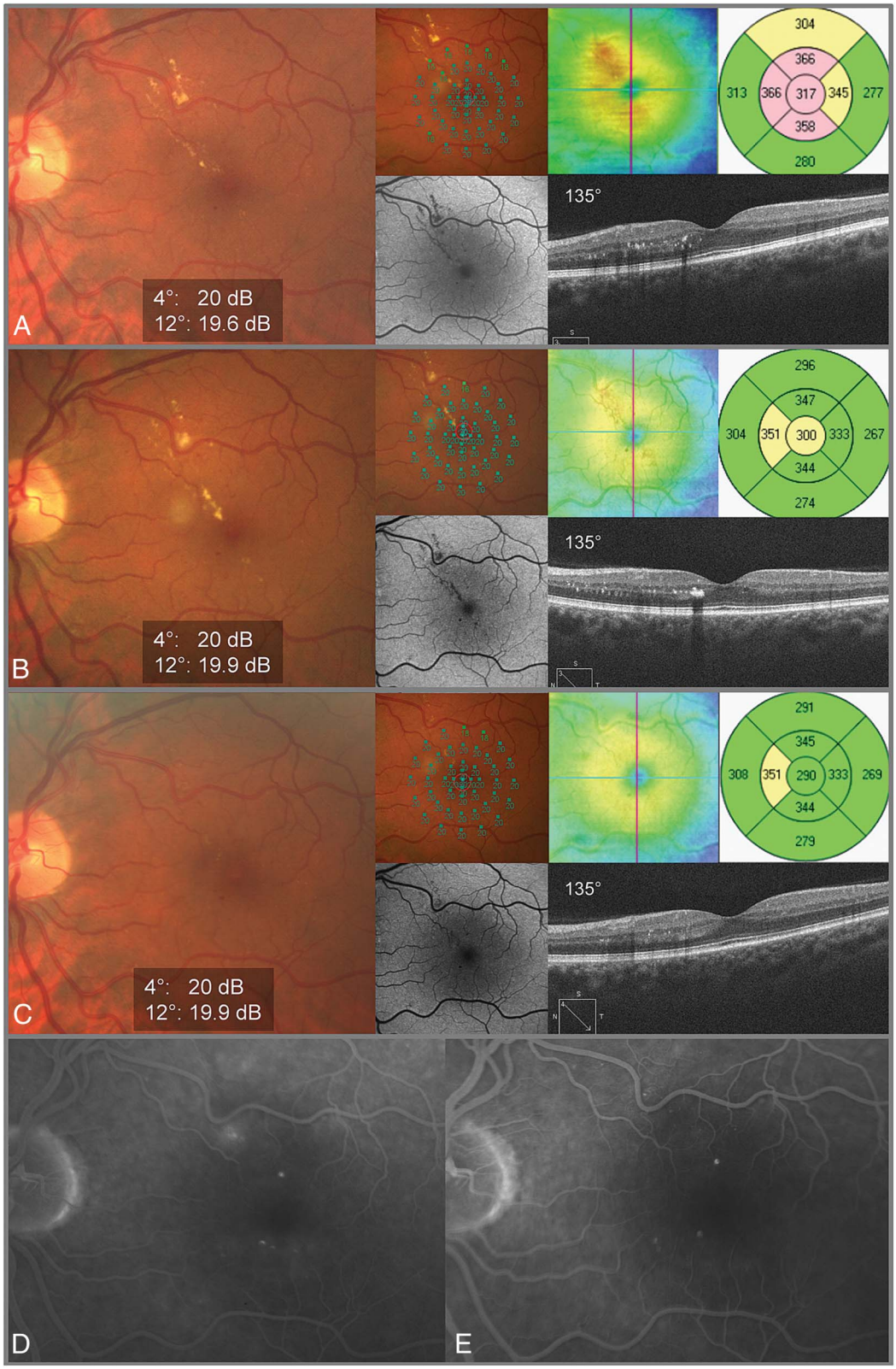

Fig. 2. Baseline (**A**), 3 months (**B**), and 6 months (**C**) of follow-up of a patient with center-involving exudative DME treated twice with infrared subthreshold micropulse diode laser (IR-MPL). **A.** Top left, color fundus photograph before D-MPL treatment. Top middle, retina sensitivity map covering central 12° obtained by microperimetry. Bottom middle, FAF. Top right, OCT retinal thickness map and SD-OCT high-definition linear scan (at 135°) before IR-MPDL treatment. **B** and **C.** Follow-up of the same patient at 3 months (**B**) and 6 months (**C**) after treatment. Color fundus

IR-MPL group ($P = 0.17$); at 3 months and 6 months, macular volume significantly decreased in the Y-MPL treatment group ($P = 0.007$ and $P = 0.006$, respectively). In the IR-MPL group, macular volume did not significantly change. There was no significant difference in macular volume at any follow-up visit between the 2 treatment groups ($P = 0.07$ and $P = 0.29$ at 3 and 6 months, respectively).

There were no changes in the integrity of the ELM or inner segment/outer segment junction in either treatment group at 3 months and 6 months of follow-up (Figures 1–3).

At baseline, mean foveal choroidal thickness was 250.7 ± 63.59 μm in the Y-MPL group and 262.75 ± 61.17 μm in the IR-MPL group ($P = 0.75$). No significant change in the foveal choroidal thickness was detected after both Y-MPL and IR-MPL treatments at 3 months or 6 months of follow-up (Figure 3).

Macular changes. No visible secondary effects of the laser spots on the retina were observed on color fundus photographs, FAF, or FA in either treatment group at 3 months and 6 months of follow-up (Figures 1 and 2).

Functional Outcomes

Visual acuity. Mean BCVA at baseline was 0.10 ± 0.12 logMAR (79.7 ± 6.1 letters ETDRS score, corresponding to 20/25 Snellen ratio) in the Y-MPL group and 0.13 ± 0.15 logMAR (78.6 ± 7.5 letters ETDRS score, approximately corresponding to 20/25 Snellen ratio) in the IR-MPL group ($P = 0.75$). There was no significant change in BCVA at each follow-up visit in either the Y-MPL (Wilcoxon signed-rank test, $P = 0.87$ at 3 months and $P = 0.96$ at 6 months) or the IR-MPL treatment group (Wilcoxon signed-rank test, $P = 0.2$ at 3 and 6 months). Best-corrected visual acuity did not significantly change between the 2 treatment groups (Y-MPL vs. IR-MPL) ($P = 0.3$ at 3 months and $P = 0.62$ at 6 months, respectively). Table 1 shows BCVA data expressed both in ETDRS score and Snellen ratios.

Microperimetry. Table 2 reports in detail all retinal sensitivity data. Briefly, at baseline, mean 4° central RS was 14.3 ± 3.3 dB in the Y-MPL group and 16.0 ± 2.8 dB in the IR-MPL group ($P = 0.1$) and mean 12° central RS was 16.0 ± 2.3 dB in the Y-MPL group and 17.0 ± 2.1 dB in the IR-MPL group ($P = 0.2$). There was a significant increase in mean central 4° RS at 3 months in the Y-MPL group (with RS $>$ 15 dB and $\leq$18 dB, $P = 0.01$) and IR-MPL group (with RS $\leq$ 15 dB, $P = 0.01$ and with RS $>$ 15 and $\leq$18 dB, $P = 0.01$) and at 6 months in the Y-MPL and IR-MPL groups (with RS $>$ 15 and $\leq$18 dB, $P = 0.01$ and $P = 0.04$, respectively). There was a significant increase in mean central 12° RS at 6 months in the Y-MPL group with RS $>$ 15 dB and $\leq$18 dB, $P = 0.047$ (Table 2). There was no significant difference in mean 4° and 12° RS between the 2 treatment groups at any follow-up visit.

Of 26 eyes treated with Y-MPL, 23 eyes (88.5%) were treated twice, whereas 3 eyes (11.5%) were treated once. Of 27 eyes treated with IR-MPL, 23 eyes (85.2%) were treated twice, whereas 4 eyes (14.8%) were treated once. The mean number of treatment spots was 287 ± 130 (range, 84–439) in the Y-MPL group and 292 ± 89 (range, 71–373) in the IR-MPL groups.

Discussion

In this study, we evaluated local safety, both morphologically and functionally, of 2 different subthreshold micropulse laser wavelengths: yellow (577 nm) and infrared (810 nm) delivered with the same duty cycle. Both yellow and infrared subthreshold micropulse lasers showed to be safe in patients with mild center-involving DME. From the morphologic point of view, no visible retinal or choroidal lesions were detected on fundus examination or any imaging modality (color fundus photos, FAF, FA, spectral domain OCT) (Figures 1–3). No changes of the integrity and reflectivity at the outer retina (external limiting membrane, inner segment/outer segment junction, RPE) were detected in this study, whereas changes in reflectivity and structure of the outer retinal layers have been always reported after modified ETDRS laser and even after other clinically invisible laser (at 532 nm).[17,18] Several authors previously reported the safety of infrared subthreshold micropulse laser at lowest duty cycle (5%) in patients with DME. Luttrull and Spink[19] reported no detectable lesions after IR-MPL on time-domain OCT. Vujosevic et al found no visible lesions on time-domain OCT, FAF, and FA.[7] The lowest duty cycle (5%) was safe, even when the treatment was performed in a "high-density" pattern.[6,7]

photograph and FAF image after IR-MPL treatment showing no retinal or RPE signs of laser treatment. Hard exudates progressively decreased over time. Microperimetry shows stable mean retinal sensitivity (ceiling effect because of the high baseline values). Optical coherence tomography retinal thickness map shows decrease in retinal thickness. No outer retinal layer changes can be seen after laser on SD-OCT linear scan. **D** and **E.** Late-phase fundus fluorescein angiogram of the same patient before (**D**) and 6 months after subthreshold IR-MPL treatment (**E**) showing a significant decrease in leaking microaneurysms. No chorioretinal laser-induced scars are visible on fundus photograph or angiographically.

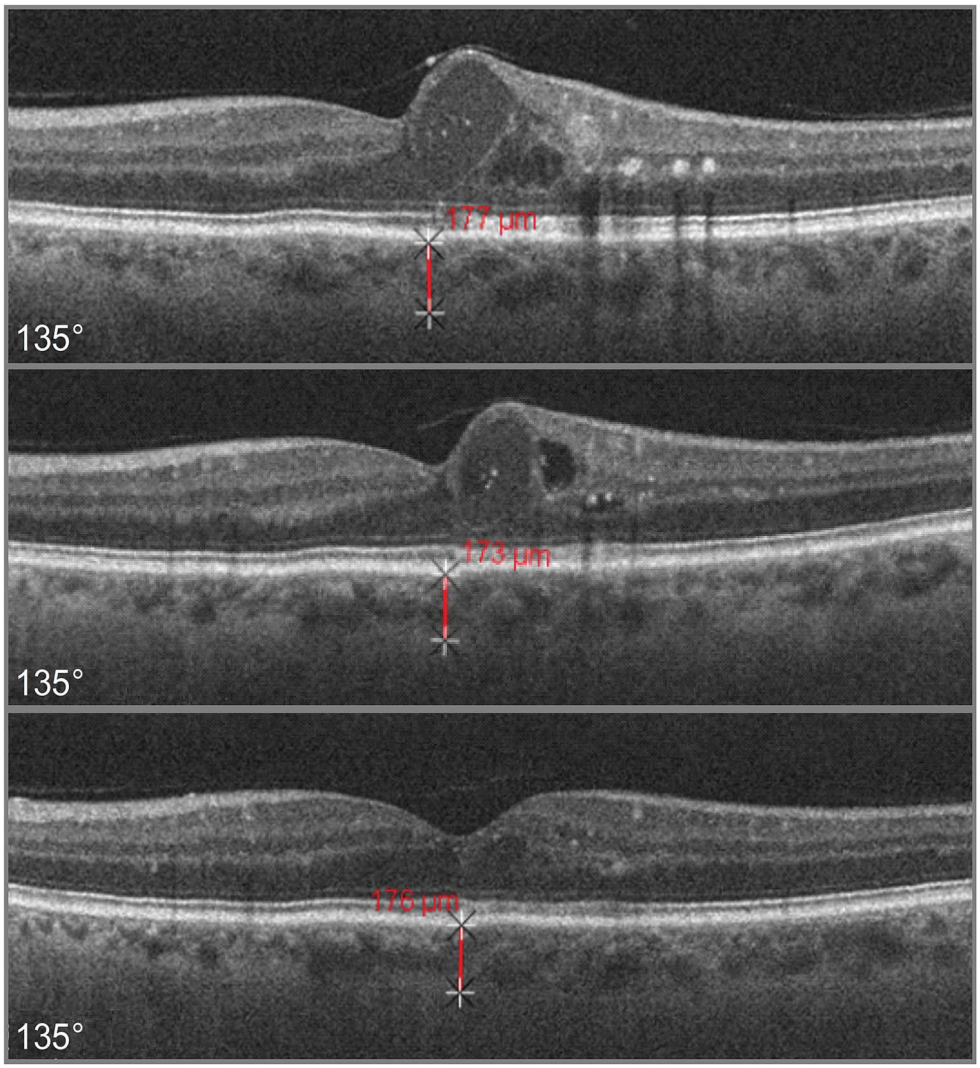

Fig. 3. High-definition spectral domain OCT of a patient with exudative DME treated with subthreshold micropulse yellow laser (Y-MPL). Top: High-definition line scan before Y-MPL treatment. Foveal choroidal thickness is determined as the perpendicular distance between the hyperreflective outer border of the RPE and the sclero–choroidal interface (moderately hyperreflective line). Foveal choroidal thickness value (177 μm, calculated by the instrument) is shown. Middle and Bottom: Follow-up of the same patient at 3 months (middle) and 6 months (bottom) after Y-MPL treatment. No outer retinal layer changes can be seen after laser on SD-OCT linear scan. Foveal choroidal thickness remains stable (173 and 176 μm).

Lavinsky et al[7] showed that the high-density treatment, which means that spots are delivered in a fully contiguous manner, is more effective in increasing BCVA and reducing retinal thickness when compared with modified ETDRS laser treatment or normal density micropulse laser treatment in DME. Even if laser spots are delivered in a fully contiguous manner, the lowest duty cycle has a wide therapeutic window without the risk for inducing retinal scars.[8,20] This is also applicable in darkly pigmented eyes.[9] Long-term data on retinal safety after IR-MPL are currently available (up to 10 years) in macular edema of retinal vascular origin.[21] Whether in the past it was theoretically considered that MPL could be performed in the fovea,[8,21] a recent study by Luttrull and Sinclair[22] confirmed the safety of the transfoveal treatment with IR-MPL in center-involving DME. In this study, we performed laser treatment in a contiguous fashion up to the edge of the foveal avascular zone, sparing the center of the fovea. The main reason for that was to perform the same treatment with both wavelengths and more easily compare Y-MPL and IR-MPL results.

A peculiar finding is that choroidal thickness in the fovea remained stable after both micropulse treatments as showed by spectral domain OCT. This finding may support the hypothesis that the site of action of both micropulse lasers is purely at the level of the RPE.

From the visual function point of view, different authors reported BCVA data after IR-MPL.[3–7,23,24] Mostly, BCVA remained stable at 6 months or 12 months after treatment.[3,4,6,23] This has been confirmed in this study.

In a previous study, Vujosevic et al[6] reported a significant increase in central retinal sensitivity (within 4 and 12 central degrees) at final follow-up visit (12 months) after IR-MPL treatment in patients with DME. In the same study, at 3 months and 6 months, no significant changes in mean retinal sensitivity were

Table 2. Macular Sensitivity of the 4 and 12 Central Degrees (Mean ± SD)

Measure	Group, dB	Laser	Baseline N	Baseline Mean ± SD, dB	3 Months After Treatment Absolute Changes Mean ± SD, dB (%)	6 Months After Treatment Absolute Changes Mean ± SD, dB (%)
MP4°	≤15	Y-MPL	13	11.6 ± 2.3	0.4 ± 2.3 (2.9)	0.3 ± 2.2 (2.3)
		IR-MPL	12	13.3 ± 1.4	**1.6[a] ± 1.8 (12.7)**	1.0 ± 1.9 (8.6)
	15–18	Y-MPL	10	16.5 ± 0.8	**0.6[b] ± 0.6 (3.9)**	**0.7[f]± 0.7 (4.5)**
		IR-MPL	6	16.8 ± 1.1	**1.1[c] ± 0.6 (6.4)**	**0.9[g] ± 0.8 (5.1)**
	>18	Y-MPL	3	18.9 ± 1.0	–0.6 ± 0.7 (–3.1)	–0.1 ± 0.4 (–0.6)
		IR-MPL	9	19.0 ± 0.5	**–0.9[d] ± 0.9 (–4.8)**	–0.4 ± 0.7 (–2.3)
	Total	Y-MPL	26	14.3 ± 3.3	0.4 ± 1.7 (2.6)	0.4 ± 1.6 (2.9)
		IR-MPL	27	16.0 ± 2.8	0.6 ± 1.7 (4.8)	0.5 ± 1.5 (4.0)
MP12°	≤15	Y-MPL	8	13.3 ± 1.7	0.3 ± 1.4 (2.0)	0.4 ± 1.0 (3.2)
		IR-MPL	5	14.1 ± 1.1	0.7 ± 1.4 (5.7)	1.1 ± 1.3 (8.5)
	15–18	Y-MPL	13	16.6 ± 0.8	0.6 ± 1.2 (3.9)	**0.6[h] ± 1.0 (4.0)**
		IR-MPL	11	16.3 ± 0.7	**0.7[e] ± 0.7 (4.0)**	–0.1 ± 0.8 (–0.8)
	>18	Y-MPL	5	18.8 ± 0.5	–0.2 ± 0.6 (–1.0)	0.1 ± 0.3 (0.4)
		IR-MPL	11	19.1 ± 0.5	–0.3 ± 0.7 (–1.6)	–0.2 ± 0.7 (–0.9)
	Total	Y-MPL	26	16.0 ± 2.3	0.4 ± 1.2 (2.4)	**0.5[i] ± 1.0 (3.7)**
		IR-MPL	27	17.0 ± 2.1	0.2 ± 1.0 (1.4)	0.1 ± 0.9 (0.6)

Comparison between yellow subthreshold micropulse laser (Y-MPL) and infrared subthreshold micropulse laser (IR-MPL) (Wilcoxon sum-rank test); significance level of absolute changes (Wilcoxon signed-rank test): [a]P = 0.016, [b]P = 0.011, [c]P = 0.012, [d]P = 0.016, [e]P = 0.019, [f]P = 0.012, [g]P = 0.044, [h]P = 0.047, [i]P = 0.029. All values are expressed in decibels. Three different groups are shown (≤15 dB, 15–18 [≤18 dB], and >18 dB).

MP4°, retinal sensitivity data within 4 central degrees determined with microperimetry; MP12°, retinal sensitivity data within 12 central degrees; dB, decibels; N, number of eyes; SD, standard deviation.

found.[6] In this study, we found an initial increase in mean 4° central retinal sensitivity as soon as 3-month follow-up in both yellow and IR-MPL groups and in the 12° central retinal sensitivity in the IR-MPL group, mainly in patients with low baseline values of mean sensitivity. This may be explained by the so-called "ceiling effect" of microperimetry technique because the increase in sensitivity in patients with near normal values cannot be accurately detected by MP1 microperimeter. Although sensitivity data in the previous[6] and this study cannot be directly compared (because study population is different, especially regarding the severity of DME and follow-up duration), we may support the hypothesis that subthreshold micropulse laser technique preserves and sometimes improves retinal sensitivity of treated retinal areas. Therefore, morphologic and visual function data reported in this study are adding new insights about safety of both yellow and IR-MPL treatments in <400 μm center-involving DME.

Major limitations of this study are short-term follow-up (up to 6 months) and the strict inclusion criteria (mild DME with high BCVA score and high mean retinal sensitivity on microperimetry). These criteria may have influenced the final results, especially regarding statistical and clinical significance. Moreover, the clinical relevance of these data can be applied just to this specific DME population (with <400 μm center-involving DME) and relatively good glycemic control.

The exact mechanism of action of MPL is still unknown and different hypotheses exist: MPL spares neurosensory retina and is selectively absorbed by the RPE, there is no loss of functional retina or inflammatory response, and MPL normalizes cytokine expression and increases therapeutic recruitment of the RPE cells.[8,20,25] Therefore, the term "retinal photostimulation" rather than retinal photocoagulation has been proposed for MPL.[8]

The safety and efficacy profiles of subthreshold micropulse laser (both IR and yellow wavelengths) are especially important in the era of intravitreal treatment for DME. In fact, in eyes with mild center-involving DME, or without center-involving DME, and with preserved visual acuity, it is essential to avoid morphologic and/or visual function macular damage, as it always happens with ETDRS laser.[26] Moreover, the use of intravitreal treatment in these patients might not be justified by its potential local and systemic complications. On the other side, the rationale to wait, without treatment, fails when coping with eyes that lately treated may have a permanent loss of visual acuity or retinal sensitivity. Therefore, the use of noninvasive and safe laser treatments may be the most suitable option in specific cases. Moreover, with a proper selection of the patients (central retinal

thickness up to 400 μm), a "one size fits all" technique may be used.[8,20] It means that with small spot diameter and lowest duty cycle (5%), the standard power settings can be applied to all patients without a need to titrate the treatment. This allows for an easy, repeatable, and safe delivering of this treatment.

Key words: diabetic macular edema, diabetic retinopathy, fluorescein angiography, fundus autofluorescence, microperimetry, laser treatment, optical coherence tomography, subthreshold micropulse laser, retinal safety.

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References

1. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985;103:1796–1806.
2. Olk RJ. Modified grid argon (blue-green) laser photocoagulation for diffuse diabetic macular edema. Ophthalmology 1986; 93:938–950.
3. Laursen ML, Moeller F, Sander B, Sjoelie AK. Subthreshold micropulse diode laser treatment in diabetic macular oedema. Br J Ophthalmol 2004;88:1173–1179.
4. Luttrull JK, Musch DC, Mainster MA. Subthreshold diode micropulse photocoagulation for the treatment of clinically significant diabetic macular oedema. Br J Ophthalmol 2005; 89:74–80.
5. Figueira J, Khan J, Nunes S, et al. Prospective randomized controlled trial comparing subthreshold micropulse diode laser photocoagulation and conventional green laser for clinically significant diabetic macular oedema. Br J Ophthalmol 2009; 93:1341–1344.
6. Vujosevic S, Bottega E, Casciano M, et al. Microperimetry and fundus autofluorescence in diabetic macular edema: subthreshold micropulse diode laser versus modified early treatment diabetic retinopathy study laser photocoagulation. Retina 2010;30:908–916.
7. Lavinsky D, Cardillo JA, Melo LA Jr., et al. Randomized clinical trial evaluating mETDRS versus normal or high-density micropulse photocoagulation for diabetic macular edema. Invest Ophthalmol Vis Sci 2011;52:4314–4323.
8. Luttrull JK, Dorin G. Subthreshold diode micropulse laser photocoagulation (SDM) as invisible retinal phototherapy for diabetic macular edema: a review. Curr Diabetes Rev 2012;8: 274–284.
9. Pankratov MM. Pulsed delivery of laser energy in experimental thermal retinal photocoagulation. Proc SPIE 1990;1202: 205–213.
10. Manjunath V, Taha M, Fujimoto JG, Duker JS. Choroidal thickness in normal eyes measured using Cirrus HD optical coherence tomography. Am J Ophthalmol 2010;150:325–329.
11. Bartsch DU, Weinreb RN, Zinser G, Freeman WR. Confocal scanning infrared laser ophthalmoscopy for indocyanine green angiography. Am J Ophthalmol 1995;120:642–651.
12. Holz FG, Bellmann C, Margaritidis M, et al. Patterns of increased in vivo fundus autofluorescence in the junctional zone of geographic atrophy of the retinal pigment epithelium associated with age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 1999;237:145–152.
13. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs–an extension of the modified Airlie House classification. ETDRS report number 10. Ophthalmology 1991;98: 786–806.
14. Ferris FL III, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol 1982;94: 91–96.
15. Vujosevic S, Casciano M. Microperimetry: technical remarks. In: Midena E, ed. Microperimetry and Multimodal Retinal Imaging. Springer-Verlag Berlin Heidelberg, Germany; 2014: 13–23.
16. Vujosevic S, Midena E, Pilotto E, et al. Diabetic macular edema: correlation between microperimetry and optical coherence tomography findings. Invest Ophthalmol Vis Sci 2006;47: 3044–3051.
17. Bolz M, Kriechbaum K, Simader C, et al; Diabetic Retinopathy Research Group Vienna. In vivo retinal morphology after grid laser treatment in diabetic macular edema. Ophthalmology 2010;117:538–544.
18. Bhatnagar A, Gibson JM, Elsherbiny S. Spectral domain optical coherence tomography can detect visible and subthreshold laser burns using 532-nm laser. Ophthalmic Surg Lasers Imaging 2010;41:e1-e3.
19. Luttrull JK, Spink CJ. Serial optical coherence tomography of subthreshold diode laser micropulse photocoagulation for diabetic macular edema. Ophthalmic Surg Lasers Imaging 2006; 37:370–377.
20. Vujosevic S, Martini F, Convento E, et al. Subthreshold laser therapy for diabetic macular edema: metabolic and safety issues. Curr Med Chem 2013;20:3267–3271.
21. Luttrull JK, Sramek C, Palanker D, et al. Long-term safety, high-resolution imaging, and tissue temperature modeling of subvisible diode micropulse photocoagulation for retinovascular macular edema. Retina 2012;32:375–386.
22. Luttrull JK, Sinclair SH. Safety of transfoveal subthreshold diode micropulse laser for fovea-involving diabetic macular edema in eyes with good visual acuity. Retina 2014;34: 2010–2020.
23. Sivaprasad S, Sandhu R, Tandon A, et al. Subthreshold micropulse diode laser photocoagulation for clinically significant diabetic macular oedema: a three-year follow up. Clin Exp Ophthalmol 2007;35:640–644.
24. Nakamura Y, Mitamura Y, Ogata K, et al. Functional and morphological changes of macula after subthreshold micropulse diode laser photocoagulation for diabetic macular oedema. Eye (Lond) 2010;24:784–788.
25. Gao X, Xing D. Molecular mechanisms of cell proliferation induced by low power laser irradiation. J Biomed Sci 2009; 16:4.
26. Bandello F, Cunha-Vaz J, Chong NV, et al. New approaches for the treatment of diabetic macular oedema: recommendations by an expert panel. Eye (Lond) 2012;26: 485–493.