SAFETY OF TRANSFOVEAL SUBTHRESHOLD DIODE MICROPULSE LASER FOR FOVEA-INVOLVING DIABETIC MACULAR EDEMA IN EYES WITH GOOD VISUAL ACUITY

JEFFREY K. LUTTRULL, MD,* STEPHEN H. SINCLAIR, MD†

Purpose: To determine the safety of transfoveal subthreshold diode micropulse laser for fovea-involving diabetic macular edema.

Methods: The records of all patients treated with transfoveal subthreshold diode micropulse laser for fovea-involving diabetic macular edema in two retina clinics were reviewed. The eligibility included fovea-involving diabetic macular edema by spectral domain optical coherence tomography and pretreatment visual acuity of 20/40 or better.

Results: Thirty-nine eyes of 27 patients aged 50 years to 87 years (mean, 69 years) were included. Postoperative follow-up ranged from 3 months to 36 months (mean, 11 months). Fourteen patients were insulin dependent, and 19 had nonproliferative retinopathy. The preoperative visual acuity was 20/20 (10 eyes), 20/25 (10 eyes), 20/30 (8 eyes), and 20/40 (11 eyes). No eye had evidence of laser-induced macular damage by any imaging means postoperatively. There were no adverse treatment effects. Logarithm of the minimum angle of resolution visual acuity was improved on average of 0.03 units at 4 months to 7 months of follow-up ($P = 0.0449$, paired t-test) and otherwise stable. The central foveal thickness was improved at 4 months to 7 months ($P = 0.05$, paired t-test) and 8 months to 12 months, postoperatively ($P = 0.04$, mixed model accounting). Maximum macular thickness was improved at 4 months to 7 months postoperatively ($P = 0.01$, paired t-test and mixed model accounting).

Conclusion: In a small retrospective series, transfoveal subthreshold diode micropulse laser was safe and effective for the treatment of fovea-involving diabetic macular edema in eyes with good preoperative visual acuity that were not the candidates for conventional photocoagulation or intravitreal injection. Further study is warranted.

RETINA 34:2010–2020, 2014

Fovea-involving diabetic macular edema (FIDME) is the most common cause of visual loss in eyes with diabetic retinopathy (DR) and the most common cause of visual disability in working-age population worldwide.[1,2] Once developed, FIDME may be difficult to eliminate with restoration of normal visual acuity.[2–4] Retinal photocoagulation has been the standard of care for the treatment of DME for decades. However, the tissue damage resulting from continuous-wave laser photocoagulation, often persistent and progressive despite reductions in treatment intensity and confinement to the outer retina by shortening exposure durations, preclude treatment in or near the fovea because of the risk of immediate or late treatment-associated visual loss.[2,4,5] Thermal retinal damage may also be reduced by laser micropulsing. However, treatment risks persist with micropulsed lasers that are operated at higher energies and/or at duty cycles at 10% or more.[6–11] Intravitreal injections of steroids and/or vascular endothelial growth factor (VEGF) inhibitors are also effective, often with better visual outcomes than with conventional photocoagulation alone or in combination with drugs.[2–4] The superiority of drug therapy over laser regarding visual acuity outcomes may be due to the

From the *Private practice, Ventura, California; and †Department of Ophthalmology, Drexel University School of Medicine, Media, Pennsylvania.

None of the authors have any financial/conflicting interests to disclose.

Reprint requests: Jeffrey K. Luttrull, MD, 3160 Telegraph Road, Suite 230, Ventura, CA 93003; e-mail: jkluttrull@gmail.com

inherent adverse effects of conventional retinal photocoagulation because photocoagulation seems at least as effective in reducing macular edema.[3] This is supported by a recent randomized clinical trial that found high-density subthreshold diode micropulse (SDM) laser treatment for treatment-naive DME to be superior to conventional photocoagulation in reducing macular thickening but with visual results comparable with intravitreal drug therapy.[11] Intraocular drug injection is problematic as well. The use of local and intravitreal steroids may cause cataract and glaucoma.[12] Vascular endothelial growth factor inhibitors are often expensive and require repeated injections over months to years to achieve and maintain an optimal effect. All intravitreal injections have a small but inherent and cumulative risk of potentially visually catastrophic endophthalmitis. Such considerations discourage intravitreal drug injection for eyes with DME with good visual acuity, that is, 20/40 or better.[3,12–16]

A particular variety of micropulsed laser application, termed "low-intensity/high-density subthreshold (810 nm) diode micropulsed laser," or "SDM," has been shown to be both effective for the treatment of DME and safe in long-term follow-up without adverse treatment effect or evidence of laser-induced retinal damage.[9,10,17,18] Although only one case of transfoveal subthreshold diode micropulse laser (TFSDM) has thus far been reported, confidence in the safety of SDM gained in over 13 years of clinical experience has led to us to the routine use of TFSDM for FIDME in our practices[17] (Figure 1). Herein, we review our experience using TFSDM for FIDME in eyes with the best preoperative visual acuities, most likely to reveal any adverse treatment effects.

Methods

This research adhered to the tenets of the Declaration of Helsinki. Institutional review board approval was obtained, and all subjects signed informed consent. The records of all patients who received treatment for FIDME in 2 vitreoretinal subspecialty practices were reviewed if TFSDM was used and if preoperative visual acuities were 20/40 or better. Fovea-involving diabetic macular edema was defined as any cystic change or thickening of the retina demonstrated by spectral domain optical coherence tomography (SD-OCT) at or within the margin of the foveal umbo resulting in inclusion of the central fovea in treatment according to the high-density/low-intensity SDM laser treatment strategy. Thus, some eyes, illustrated by Figure 2, had neither measurable foveal thickening nor visual loss preoperatively. Eyes were excluded from the study if they had intraocular surgery within 6 months of treatment, extrafoveal SDM within 4 months before TFSDM, postoperative follow-up of less than 3 months, treatment with intravitreal or local steroids within 4 months or VEGF inhibitors within 1 month before SDM treatment, absence of adequate preoperative or postoperative diagnostic imaging, confounding macular disease such as epiretinal membrane, vitreomacular traction, or age-related macular degeneration, or confounding systemic

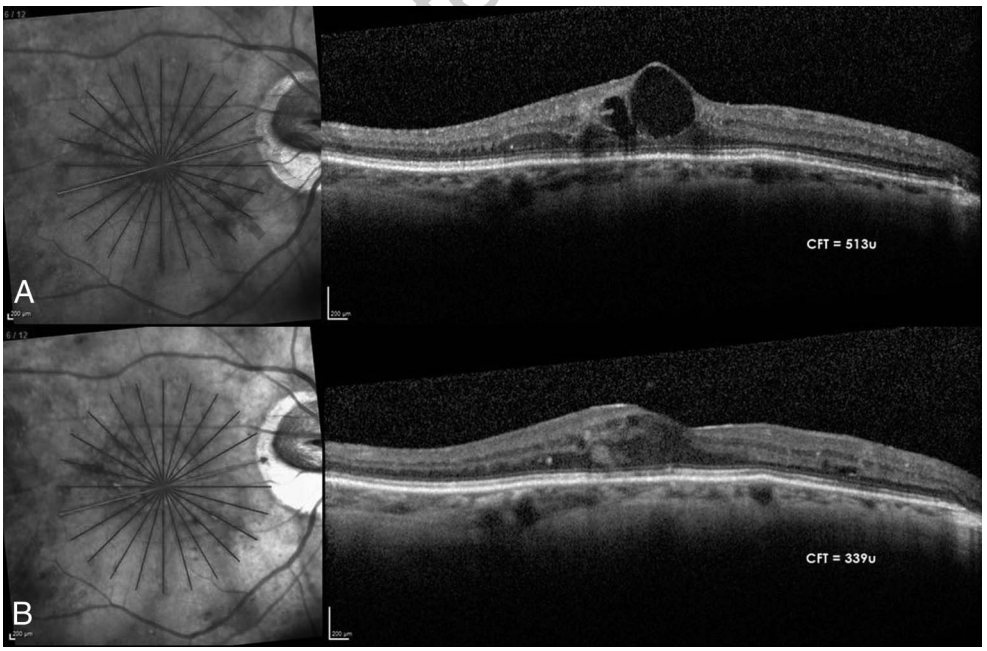

Fig. 1. Fovea-involving diabetic macular edema before (**A**) and 3 months after (**B**) TFSDM laser treatment. Preoperative visual acuity of 20/50. Visual acuity of 20/40 3 months postoperatively. (Fundus photographs on left depict SD-OCT scan positions and location of scans shown on right).

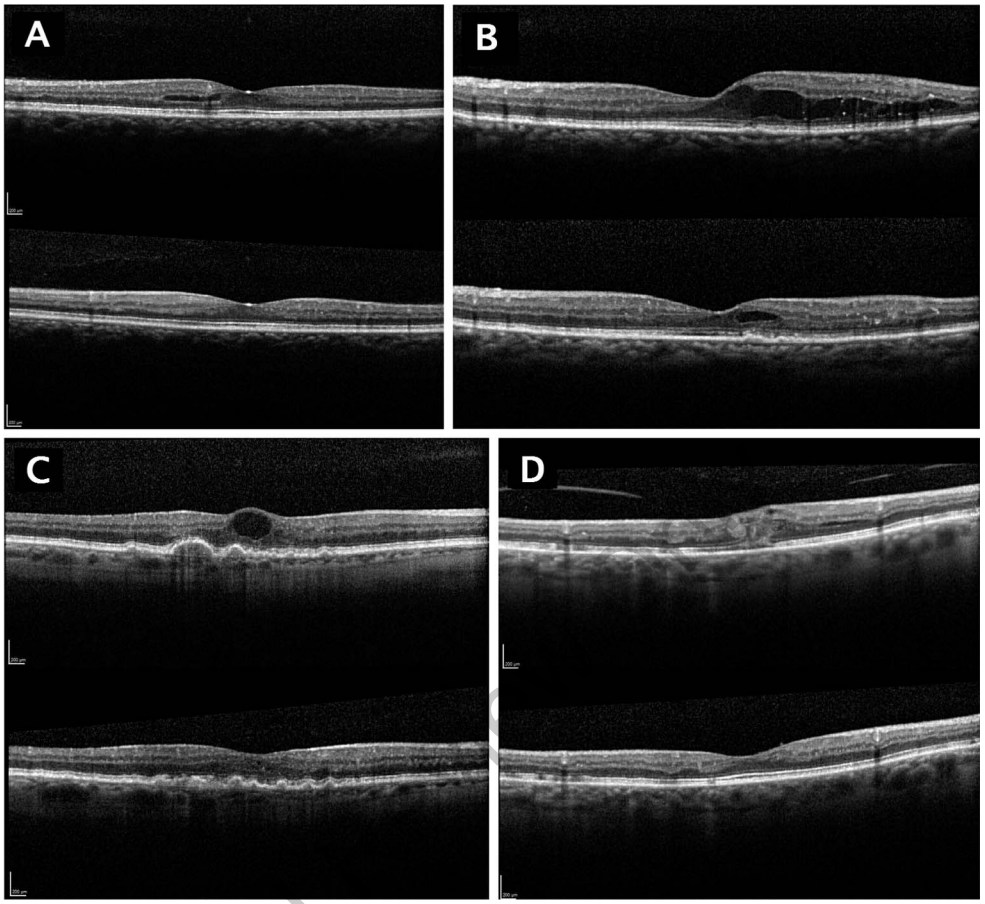

Fig. 2. Types of FIDME in eyes with visual acuity of 20/40 or better treated with TFSDM in this study (In each pair, A-D, top of the frames represent preoperative SD-OCT and bottom of the frames represent postoperative SD-OCT). **A.** Intrafoveal cysts without retinal thickening. **B.** Intrafoveal thickening with minimal central foveal thickening. **C.** Isolated central foveal cyst. **D.** Diffuse macular thickening including the fovea.

disease including uncontrolled hypertension (>160/>110) or uncontrolled diabetes (fasting blood glucose level of >300 mg/dL on 2 or more occasions postoperatively or HbA1c ≥ 10%).

All eyes that were treated with SDM laser parameters demonstrated to be both clinically effective and harmless. These parameters include the use of a micropulsed 810-nm diode laser (Oculight SLX; Iridex Corp, Mountain View, CA), small retinal spot (125–200 μm), 5% duty cycle, and power and pulse duration sufficient to achieve an American National Standards Institute (ANSI) "maximum permissible exposure" power delivery of approximately 40–50× maximum permissible exposure.[9,10,17,18] In all cases, standard SDM was performed consisting of high-density placement of contiguous and confluent laser spots over the entire area of macular edema, including the fovea indicated by preoperative SD-OCT (Clinics 1 and 2) and macular leakage by fundus fluorescein angiogram (Clinic 2). Within each clinic, the same SDM laser parameters were used for all eyes without individual adjustment for lens status, vitreous opacity, fundus coloration, retinal hemorrhage, or degree or location of macular thickening.[9,10,17,18] In Clinic 1, the following laser parameters were used for all patients: 125 μm spot, 0.95 W power, 0.3-second duration, and 5% duty cycle; or 200 μm spot, 1.4 W power, 0.3-second duration, and 5% duty cycle (both 54 × American National Standards Institute [ANSI] maximum permissible exposure). In Clinic 2, laser parameters for all patients were: 125 μm spot, 0.78 W power, 0.3-second duration, and 5% duty cycle (or 47 × ANSI maximum permissible exposure).[9,10]

All eyes were evaluated preoperatively and postoperatively by SD-OCT (Clinic 1: Spectralis, Heidelberg Engineering, Heidelberg, Germany; and Clinic 2: OPKO, Miami, FL), fundus photography including red-free, infrared, and fundus autofluorescence photography, and fundus fluorescein angiogram. Diabetic macular edema was assessed by SD-OCT measurement of central foveal thickness (CFT), representing the maximum apical thickness at the center of the fovea, and maximum macular thickness (MMT), representing the maximum retinal thickness within 1.5 mm of the foveal center. Postoperative MMT measurements were taken at the same point as the preoperative MMT measurement. The presence of intrafoveal cysts without visual loss or retinal thickening by SD-OCT was also an indication for TFSDM treatment (Figure 2).

Data Analysis

Sample characteristics were summarized using mean values and standard deviations for continuous variables and frequencies and percentages for categorical variables. Because of the small sample size, all eyes were considered independent in analyses. Preoperative to postoperative comparisons were tested using paired *t*-tests or Wilcoxon signed-rank tests (when small sample sizes or nonnormal data were present) at uniform intervals up to 16 months postoperatively (3 months, 4–7 months, 8–12 months, and 13–16 months). Subgroup analyses were performed on eyes with preoperative CFT < 300 μm, CFT ≥ 300 μm, MMT < 350 μm, and MMT ≥ 350 μm. Visual acuities were converted to logMAR units for statistical analysis, and a 45 μm addition was made to SD-OCT results obtained from the OPKO SD-OCT to make these measures comparable with the Spectralis SD-OCT results.[19] All analyses were performed with SAS statistical software (version 9.3, Cary, NC).

Results

Demographics

A total of 39 eyes of 27 subjects were identified for study having met the inclusion criteria. Fifteen subjects contributed only 1 eye, and 12 subjects contributed both eyes to the study. Table 1 provides descriptive statistics of the study sample. The age of the subjects ranged from 50 years to 87 years at the time of TFSDM treatment (mean, 69 years), and their postoperative follow-up ranged from 3 months to 36 months (mean, 11 months). Fourteen patients had insulin-dependent diabetes. Eight eyes had been previously treated with panretinal laser treatment for proliferative diabetic retinopathy. Seven eyes had previous treatment with intravitreal VEGF inhibitors and/or steroids. No eyes were treated medically by intravitreal or local injection postoperatively. Of the 39 eyes, 19 (49%) were treated only once. Retreated eyes included 14 eyes retreated at 3 months, 5 eyes at 4 months to 7 months, and 1 eye at 8 months to 12 months after the initial treatment.

Differences Between Clinics 1 and 2

Clinic 1 contributed 19 eyes of 15 subjects to the sample, and Clinic 2 contributed 20 eyes of 12 subjects. Demographically, subjects from Clinic 2 were significantly older, and eyes had significantly less severe disease than those from Clinic 1, with better logMAR visual acuity, thinner normalized CFT and MMT, and fewer subjects with proliferative diabetic retinopathy (data not shown). Despite significant entry in demographic and clinical differences at presentation, there were no significant treatment outcome differences (change in logMAR visual acuity, CFT, or MMT) between Clinic 1 and Clinic 2.

Table 1. Sample Characteristics

	Sample (39 Eyes of 27 Subjects)		
Continuous Variables	N	Mean (SD)	Minimum–Maximum
Eye-based			
Number of previous IVA	35	0.7 (1.9)	0–10
Number of SDM laser applications	39	640.1 (195.7)	329–1400
logMAR VA	39	0.15 (0.12)	0.00–0.30
Normalized CFT	39	298.5 (103.4)	145–655
Normalized MMT	39	404.9 (75.1)	295–625
Person-based			
Age at surgery*	27	68.5 (10.1)	49.7–86.7
Categorical Variables			Frequency (%)
Eye-based			
VA			
20/20			10 (25.6)
20/25			10 (25.6)
20/30			8 (20.5)
20/40			11 (28.2)
Spot size			
125			30 (76.9)
200			9 (23.1)
Person-based			
Diabetes type			
1			14 (51.9)
2			13 (48.2)
Diabetic retinopathy status			
NPDR			19 (70.4)
PDR			8 (29.6)
Hypertension			
Yes			17 (63.0)
No			10 (37.0)

*First surgery in subjects who contributed both eyes.
IVA, intravitreal anti-VEGF injection; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; SD, standard deviation; VA, visual acuity.

Safety

There was no evidence of laser effect or injury to the retinal pigment epithelium (RPE) or neurosensory retina by any imaging method (clinical examination, infrared fundus photography, red-free fundus photography, fundus autofluorescence photography, fundus fluorescein angiogram, or SD-OCT) at any time in any eye postoperatively, other than reduction in the retinal thickness or resolution of intraretinal cysts demonstrated by SD-OCT. There were no adverse treatment effects or complications (Figures 3–5).

Visual Acuity

Preoperative visual acuities were 20/20 (10 eyes), 20/25 (10 eyes), 20/30 (8 eyes), and 20/40 (11 eyes).

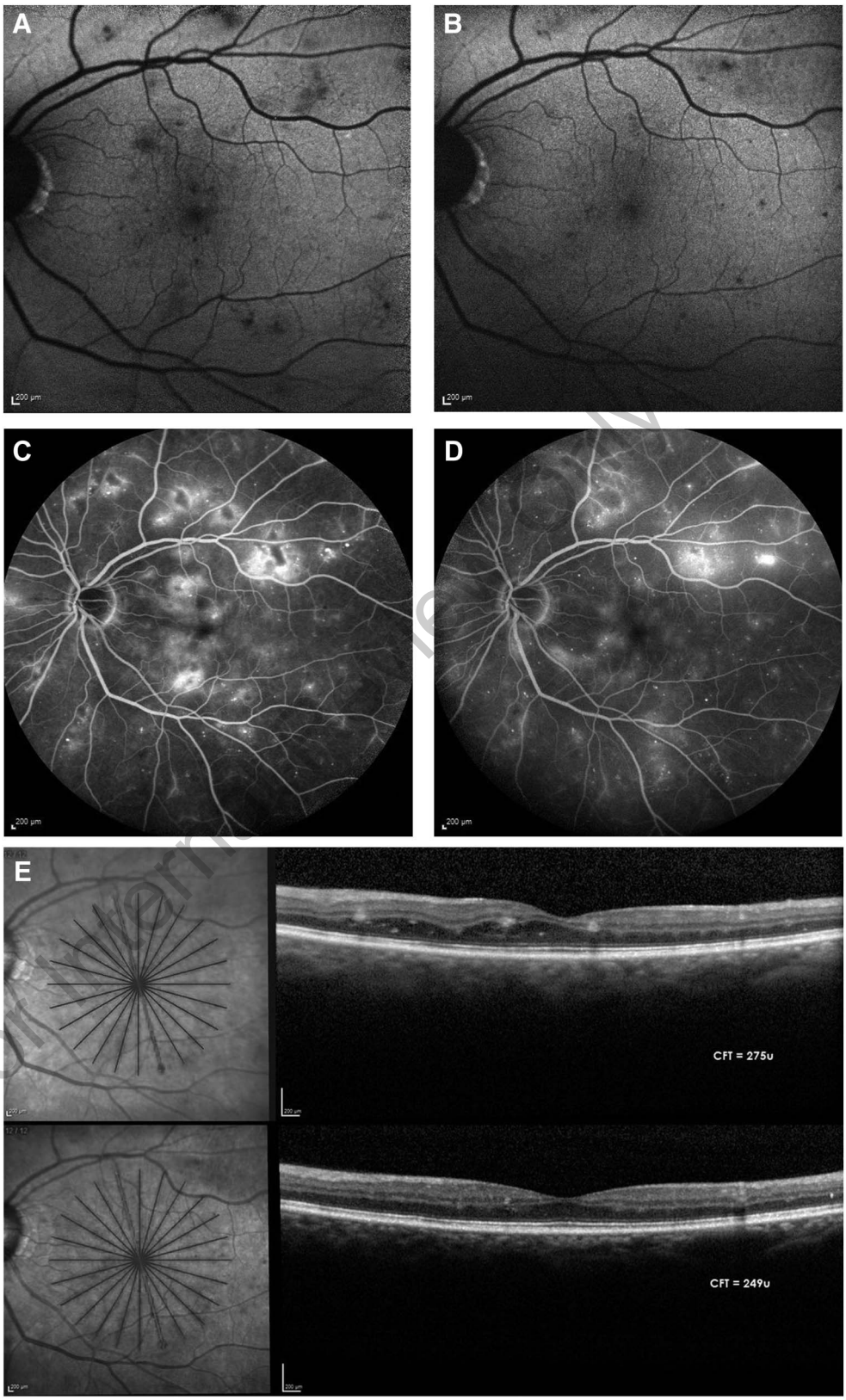

Fig. 3. Fundus autofluorescence photograph of the left eye with FIDME before (**A**) and after (**B**) TFSDM. Note the reduction in local retinopathy and absence of laser-induced retinal damage. Intravenous fundus fluorescein angiogram before (**C**) and after (**D**) TFSDM for FIDME. Note the reduced macular leakage and absence of laser-induced retinal damage. **E.** SD-OCT before (above) and after (below) TFSDM for FIDME. Note the reduction in the macular thickening and absence of evidence of laser-induced retinal damage. (Fundus photographs on left depict SD-OCT scan positions and location of scans shown on right).

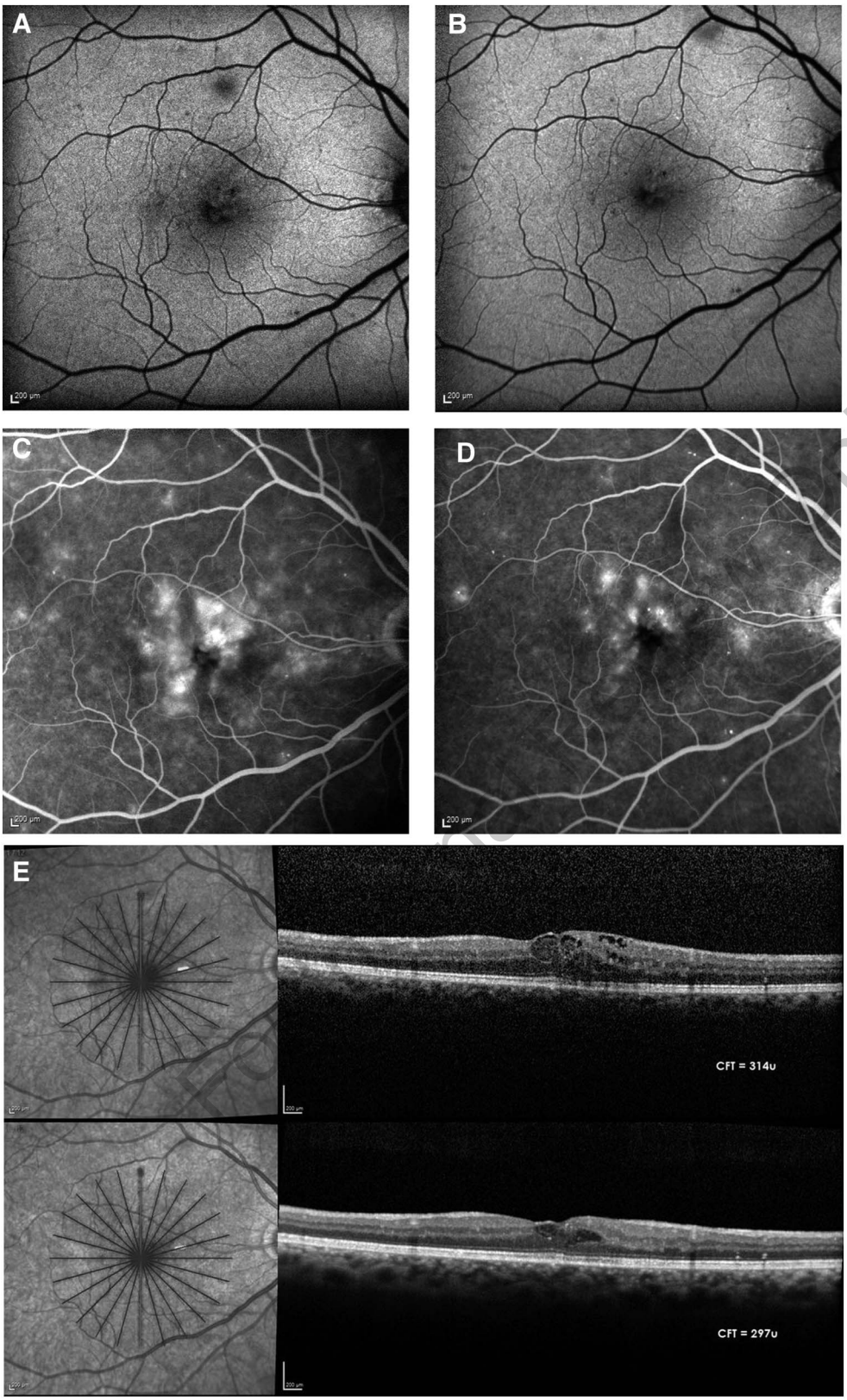

Fig. 4. Fundus autofluorescence photography of the right eye with FIDM and cystoid macular edema (CME) before (**A**) and after (**B**) TFSDM. Note the reduction in CME and absence of laser-induced retinal damage. Fundus fluorescein angiogram before (**C**) and after (**D**) TFSMD for FIDME. Note the reduced macular leakage and absence of laser-induced retinal damage. **E.** Spectral domain optical coherence tomography before (above) and after (below) TFSDM for FIDME. Note the reduced macular thickness and absence of laser-induced retinal damage. (Fundus photographs on left depict SD-OCT scan positions and location of scans shown on right).

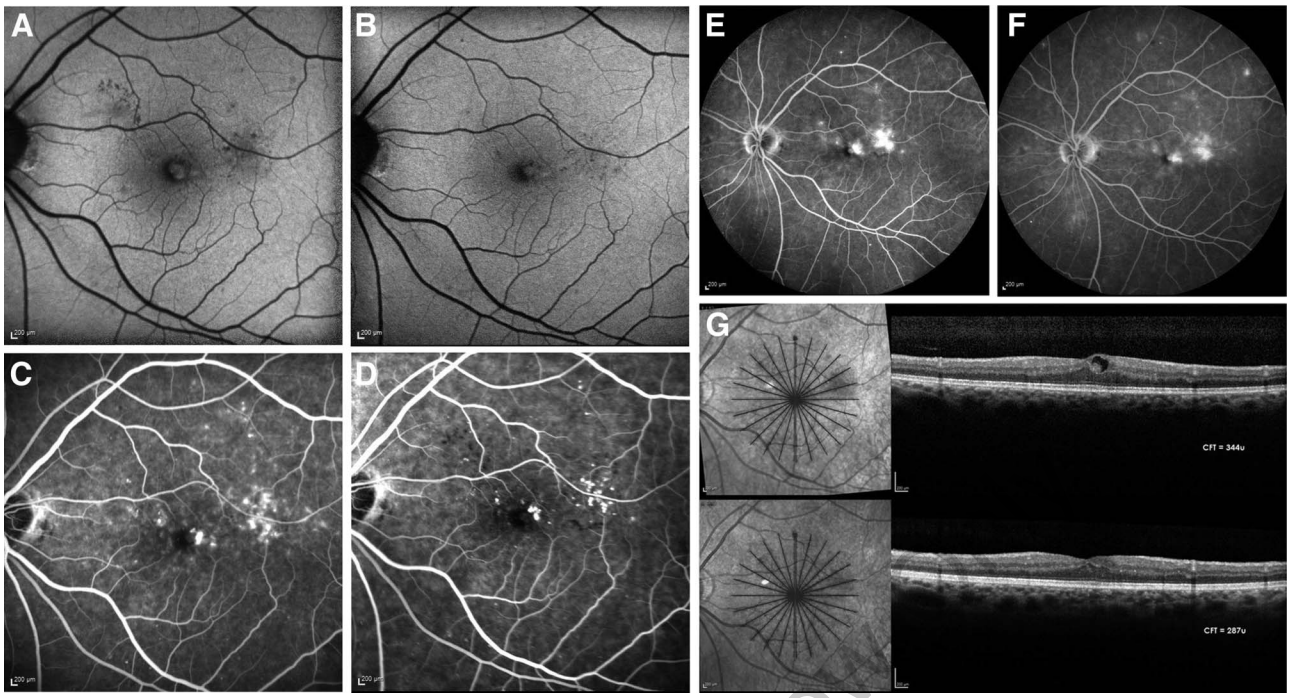

Fig. 5. Fundus autofluorescence photography of the left eye with FIDME and foveal cyst before (**A**) and after (**B**) TFSDM for FIDME. Note the reduction in maculopathy and foveal cyst after treatment without laser-induced retinal damage. Early phase fundus fluorescein angiogram before (**C**) and after (**D**) TFSDM for FIMDE. Note the absence of laser-induced retinal damage. Late phase fundus fluorescein angiogram before (**E**) and after (**F**) TFSDM for FIDME. Note the reduction in macular leakage. (**G**) Spectral domain optical coherence tomography before (above) and after (below) TFSMD for FIDME. Note the reduced macular thickening and absence of laser-induced retinal damage. (Fundus photographs on left depict SD-OCT scan positions and location of scans shown on right).

Postoperatively, there were no cases of treatment-associated subjective or measured vision loss. Many patients reported subjective visual improvement within days after the treatment.

Preoperative and postoperative logMAR visual acuities are summarized in Table 2. Overall, the visual acuity remained stable throughout the course of follow-up, with a significant improvement noted at 4 months to 7 months postoperatively (average logMAR improvement = 0.03 units; $P = 0.0449$, paired t-test).

All subgroups of eyes, including those presenting with CFT $\leq$ 300 μm (n = 24), CFT $\geq$ 300 μm (n = 15), MMT $\leq$ 350 μm (n = 11), and MMT $\geq$ 350 μm (n = 28), showed stable logMAR visual acuity postoperatively.

Central Foveal Thickness

Table 3 and Figure 4, A–C summarize preoperative and postoperative CFT measures. Overall, CFT ranged from 145 μm to 655 μm (mean, 299 μm) preoperatively, and a marginally significant decrease was present at 4 months to 7 months postoperatively (average decrease = 32.0 μm; $P = 0.0525$, paired t-test) (Figures 3–5).

For eyes presenting with CFT $<$ 300 μm, CFT was marginally improved at 3 months (average decrease = 12 μm; $P = 0.0542$) and significantly improved at 4 months to 7 months postoperatively (average decrease = 17 μm; $P = 0.0041$, Wilcoxon signed-rank test). In eyes presenting with CFT $\geq$ 300 μm, no significant differences between preoperative and postoperative CFT were found.

Maximum Macular Thickness

Table 4 and Figure 5, A–C summarize the preoperative and postoperative MMT measures. Overall, MMT ranged from 295 μm to 625 μm (mean, 405 μm) preoperatively, with a significant decrease measured at 4 months to 7 months postoperatively (average decrease = 19 μm; $P = 0.0100$, paired t-test) (Figures 3–5).

For eyes presenting with MMT $<$ 350 μm, no significant change in MMT from preoperative measurement was seen at any time postoperatively. In eyes presenting with MMT $\geq$ 350 μm, MMT was significantly reduced at 4 months to 7 months postoperatively (average decrease = 24 μm; $P = 0.0178$, Wilcoxon signed-rank test).

Holm's Adjustment

To address the multiple tests performed and reduce the possibility of finding a significant result by chance alone, we also used Holm's adjustment for the same tests performed at the 4 different time points. This

Table 2. Preoperative to Postoperative Change in logMAR Visual Acuity

	Preoperative logMAR*		Postoperative logMAR		Change		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	P†
Overall sample (n = 39 eyes)							
3 months	31	0.14 (0.11)	31	0.15 (0.12)	31	0.01 (0.09)	
4–7 months	34	0.15 (0.12)	34	0.12 (0.11)	34	−0.03 (0.09)	0.0449
8–12 months	20	0.17 (0.13)	20	0.14 (0.12)	20	−0.03 (0.11)	0.2348
13–16 months	15	0.19 (0.11)	15	0.16 (0.09)	15	−0.03 (0.09)	0.1804
Presenting CFT $<$ 300 μm sample (n = 24)							
3 months	19	0.11 (0.11)	19	0.10 (0.12)	19	−0.00 (0.07)	0.9297
4–7 months	20	0.11 (0.13)	20	0.09 (0.12)	20	−0.02 (0.10)	0.4063
8–12 months	10	0.10 (0.12)	10	0.10 (0.15)	10	0.01 (0.13)	0.8750
13–16 months	6	0.13 (0.12)	6	0.09 (0.06)	6	−0.03 (0.13)	0.6250
Presenting CFT $\geq$ 300 μm sample (n = 15)							
3 months	12	0.20 (0.10)	12	0.23 (0.08)	12	0.03 (0.11)	0.8750
4–7 months	14	0.21 (0.10)	14	0.16 (0.08)	14	−0.05 (0.09)	0.1094
8–12 months	10	0.24 (0.08)	10	0.18 (0.07)	10	−0.07 (0.08)	0.0625
13–16 months	9	0.24 (0.08)	9	0.20 (0.08)	9	−0.04 (0.08)	0.5000
Presenting MMT $<$ 350 μm sample (n = 11)							
3 months	8	0.06 (0.05)	8	0.07 (0.06)	8	0.01 (0.03)	1.0000
4–7 months	8	0.07 (0.10)	8	0.05 (0.07)	8	−0.03 (0.13)	0.7500
8–12 months	4	0.02 (0.05)	4	0.02 (0.05)	4	0.00 (0.08)	1.0000
13–16 months	1	0.00 (—)	1	0.00 (—)	1	0.00 (—)	NA
Presenting MMT $\geq$ 350 μm sample (n = 28)							
3 months	23	0.17 (0.12)	23	0.18 (0.12)	23	0.01 (0.10)	0.9333
4–7 months	26	0.17 (0.12)	26	0.14 (0.11)	26	−0.04 (0.08)	0.0869
8–12 months	16	0.21 (0.11)	16	0.17 (0.12)	16	−0.04 (0.12)	0.2188
13–16 months	14	0.21 (0.10)	14	0.17 (0.08)	14	−0.04 (0.10)	0.1875

*In the subset of eyes with corresponding postoperative measures.
†Paired *t*-test or Wilcoxon signed-rank test. None remain significant after Holm's adjustment for multiple testing.
CFT, central foveal thickness; MMT, maximum macular thickness; SD, standard deviation; NA, not applicable.

reduced the significance of some of our findings (Tables 2–4), but the average values (logMAR visual acuity, CFT, and MMT) continued to show a trend for improvement.

Discussion

There are several reasons to consider laser treatment of the fovea in DME. First, FIDME is the main cause

Table 3. Preoperative to Postoperative Change in Normalized CFT

	Preoperative CFT*		Postoperative CFT		Change		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	P†
Overall sample (n = 39 eyes)							
3 months	33	310.9 (104.5)	33	312.3 (126.9)	33	1.4 (40.2)	0.8467
4–7 months	33	304.8 (109.4)	33	272.7 (96.4)	33	−32.0 (91.4)	0.0525
8–12 months	17	329.4 (88.8)	17	305.5 (105.9)	17	−23.9 (64.1)	0.1441
13–16 months	15	332.1 (92.7)	15	314.1 (112.5)	15	−18.0 (58.9)	0.2565
Presenting CFT $<$ 300 μm sample (n = 24)							
3 months	19	241.4 (33.8)	19	229.2 (35.9)	19	−12.2 (22.9)	0.0542
4–7 months	20	233.3 (36.5)	20	216.2 (34.1)	20	−17.1 (22.3)	0.0041‡
8–12 months	8	250.1 (28.3)	8	236.3 (57.2)	8	−13.9 (40.6)	0.2500
13–16 months	7	248.3 (27.8)	7	229.4 (34.3)	7	−18.9 (24.7)	0.0625
Presenting CFT $\geq$ 300 μm sample (n = 15)							
3 months	14	405.4 (92.8)	14	425.1 (118.4)	14	19.8 (51.2)	0.2671
4–7 months	13	414.8 (90.4)	13	359.7 (97.1)	13	−55.1 (143.3)	0.1140
8–12 months	9	399.9 (56.6)	9	367.1 (102.5)	9	−32.8 (81.1)	0.3125
13–16 months	8	405.4 (57.9)	8	388.1 (104.2)	8	−17.3 (80.1)	0.7422

*In the subset of eyes with corresponding postoperative measures.
†Paired *t*-test or Wilcoxon signed-rank test.
‡Remains significant after Holm's adjustment for multiple testing.
SD, standard deviation.

Table 4. Preoperative to Postoperative Change in Normalized MMT

	Preoperative MMT*		Postoperative MMT		Change		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	P†
Overall sample (n = 39 eyes)							
3 months	33	418.2 (73.7)	33	419.5 (83.9)	33	1.3 (40.2)	0.8568
4–7 months	33	412.5 (78.2)	33	393.8 (74.4)	33	−18.8 (39.4)	0.0100‡
8–12 months	17	417.2 (64.9)	17	406.2 (67.3)	17	−11.0 (50.2)	0.3793
13–16 months	16	413.8 (65.7)	16	402.9 (59.5)	16	−10.9 (42.3)	0.3205
Presenting MMT $<$ 350 μm sample (n = 11)							
3 months	6	333.3 (13.4)	6	335.0 (18.7)	6	1.7 (17.7)	0.9688
4–7 months	8	327.5 (17.5)	8	323.8 (15.5)	8	−3.8 (13.0)	0.5938
8–12 months	2	320.0 (7.1)	2	315.0 (28.3)	2	−5.0 (35.4)	1.0000
13–16 months	2	320.0 (7.1)	2	315.0 (28.3)	2	−5.0 (35.4)	1.0000
Presenting MMT $\geq$ 350 μm sample (n = 28)							
3 months	27	437.0 (68.0)	27	438.2 (81.1)	27	1.2 (43.9)	0.8041
4–7 months	25	439.7 (69.9)	25	416.2 (71.8)	25	−23.6 (43.8)	0.0178
8–12 months	15	430.2 (57.3)	15	418.4 (61.4)	15	−11.8 (52.7)	0.4243
13–16 months	14	427.1 (58.6)	14	415.4 (51.7)	14	−11.7 (44.3)	0.2729

*In the subset of eyes with corresponding postoperative measures.
†Paired *t*-test or Wilcoxon signed-rank test.
‡Remains significant after Holm's adjustment for multiple testing.
SD, standard deviation.

of vision loss in working-aged population with diabetes mellitus. Because diabetes mellitus is a rapidly growing pandemic, the costs associated with visual disability because of DME are great to individuals, society, health care systems, and economies worldwide.[1–3,14] Second, it has long been established that the application of laser treatment to an area of DME tends to reduce retinal thickening in that area and the risk of subsequent visual acuity loss. In some, retinal photocoagulation may also improve visual acuity.[2,4,20] Third, the RPE is known to be an important mediator of DR and DME through elaboration of a many extracellular chemical factors both known and unknown, including VEGF, which are particularly potent locally. Because RPE density is maximal in the fovea, any treatment strategy directed at influencing the behavior of the RPE (such as SDM) in the treatment of FIDME would thus be expected to be most effective applied to the foveal RPE.[17,20,21] Finally, complete coverage of the entire area of DME with high-density laser application is a cornerstone of SDM theory and practice.[10,17] This echoes the Early Treatment Diabetic Retinopathy Study finding that increased treatment area and density improved results, and the Arrhenius principle, which states that many low-intensity laser applications can produce the same biologic effect as few high-intensity laser applications.[2,4,17,22,23] As the only risk of SDM is under treatment, inclusion of the fovea in FIDME allows more treatment to be applied to the dysfunctional macula, which maximizes the treatment benefit. A randomized clinical trial has confirmed the superiority of high-density micropulse laser application compared with both conventional low-density modified Early Treatment Diabetic Retinopathy Study and micropulse laser treatment for DME regarding both macular thickness reduction and visual acuity improvement.[11]

There are several reasons to prefer treatment of diabetic macular disease prior to visual loss or measurable macular thickening.[2,4] First, retinal function and physiologic testing demonstrate diabetes-induced retinal dysfunction early in the disease and long before the development of clinical retinopathy.[20,23,24] Second, early treatment of any chronic progressive disease tends to ease management and reduces disease morbidity. Symptomatic and/or visually threatening DME begins as asymptomatic disease, initially associated with normal visual acuity and macular abnormalities below the threshold of biomicroscopic and SD-OCT resolution because physiologic dysfunction precedes morphologic change. Once developed, FIDME is usually associated with central vision loss. Visual acuity improvement in such eyes is often difficult to achieve with any treatment modality, and restoration and maintenance of normal visual acuity is uncertain if not unlikely.[2–4,13] Thus, optimal treatment of DME would address diabetic foveal dysfunction before the development of FIDME and vision loss to foster the best long-term visual outcome.

Thus, although there are reasons to recommend early treatment of the diabetic fovea with good visual acuity, there is only one argument against it, risk. Conventional photocoagulation is inherently destructive, risking both immediate and long-term loss of visual acuity because of the loss of functional tissue, inflammation, and

secondary scar formation and fibrosis that often worsens with time.[2,4,25,26] Although short-pulse continuous-wave lasers may confine laser-induced damage to the outer retina and/or RPE, even such limited damage again recommends against its use near, or within, the fovea.[5] Micropulsed lasers may also reduce thermal retinal damage, but the clinical effect depends entirely on the application parameters, with higher energies, especially duty cycles over 5%, rapidly approaching the clinical behavior and risk profile of continuous-wave lasers. Thus, the conventional high-intensity (15% duty cycle)/low-density (modified grid) laser treatment stratagem for DME used by Figueira et al and others continued to demonstrate micropulse laser-induced thermal retinal damage precluding both high-density and intrafoveal treatment.[6–9,17,22] Periocular and intravitreal steroids can be effective but short-lived and associated the risks of cataract, glaucoma, and infection, as well as adverse effects such as pain and redness at the injection sites.[12] Intravitreal VEGF inhibitors are also effective but also have inherent risks and adverse effects including endophthalmitis, pain, and redness at injection sites, and high cost and burdensome administration generally that require repeated and long-term treatment to maintain optimal effectiveness.[3,12–16] Thus, none offers a feasible or compelling approach to early treatment of diabetic foveal dysfunction in eyes with good visual acuity.

Low-intensity/high-density SDM is a subtype of micropulse laser treatment effective in the treatment of DME, and it is uniquely intended and demonstrated to be free from evidence of harm or adverse effect in long-term follow-up. Although the absence of a treatment end point that is clinically detectable by current technology precludes precise individual treatment optimization and titration, the exceptionally wide therapeutic window of SDM allows treatment with known laser parameters shown to be both clinically effective and safe in long-term follow-up.[9,10,17,18,22] The absence of adverse treatment effect allows safe use of SDM within the fovea.[9,17] Clearly, eyes with good preoperative visual acuity and minimal anatomical abnormality would be most likely to exhibit adverse treatment effects related to transfoveal laser application and least likely to demonstrate treatment benefits. However, in this series from two clinics, TFSDM was safe in such eyes, without any evidence of laser-induced retinal damage or adverse effect. Furthermore, TFSDM was found to improve DME indices while stabilizing or improving visual acuity postoperatively. Although this study is small and retrospective, our results are consistent with current conceptions of diabetic eye disease, computational and empirical models of laser/retinal interactions, and the results from over 13 years of clinical experience with SDM, published clinical reports, and randomized trials, all of which have demonstrated effective treatment of DME in the absence of complications, adverse treatment effects, laser-induced retinal damage, or treatment-associated visual loss.[9–11,17,18,22,26]

It is important to note that many eyes treated in this study, illustrated by Figure 2, could be clinically improved, thus reducing the risk of vision loss due to DME with little to no measurable reduction in macular edema indices or improvement in logMAR visual acuity because these were normal or near-normal preoperatively. However, we believe that such eyes represent the best opportunity to intervene to prevent vision loss from DME and that SDM seems uniquely suited to that task. Because the trend progresses from DME treatment indications based on biomicroscopy ("clinically significant" DME) to newer high-resolution retinal imaging and other diagnostic technologies, new signals and descriptors for diabetic macular dysfunction will be developed to better define treatment indications and outcomes.[2,9,27] We expect that these indicators will be physiologic rather than anatomical, noting that even "early" or "mild" nonproliferative diabetic retinopathy actually represents advanced disease with endorgan damage caused by chronic physiologic dysfunction.[2,4,23]

Micropulsed lasers are currently available in several different wavelengths. We believe that the 810-nm wavelength is ideal for both safe and effective SDM laser treatment within the fovea.[9,17,22] The micropulsed 810-nm wavelength is maximally absorbed by the RPE. It is minimally scattered and has negligible absorption by media opacity, such as cataract or vitreous hemorrhage, and not absorbed by intraretinal hemorrhage, retinal vessels, or foveal luteal pigment, nor it is absorbed or attenuated by thickened neurosensory retina.[22] These characteristics and the wide therapeutic range when administered with a low micropulse duty cycle eliminate, in most patients, the need for clinical adjustment of laser parameters to accommodate individual variations in lens or media status, fundus coloration, or DME severity.[9,10,17,18] Thus, inadvertent laser damage, a critical concern because of the "high-density" treatment strategy of SDM, particularly in the fovea, is reliably precluded.[10] Such confidence in treatment safety permits the use of SDM within the fovea. Shorter wavelengths such as 577 nm (yellow) and 532 nm (green) for micropulsed retinal laser treatment currently have less well-defined safety and efficacy information. Shorter wavelengths may pose increased risk of inadvertent retinal damage because of increased scatter and media absorption, requiring retinal patient-specific adjustment of laser parameters that are difficult to titrate because of the absence of a visible treatment end point. Finally, shorter wavelengths are

more energetic. Thus, shorter laser wavelengths proportionally narrow the therapeutic window, further increasing the risk of inadvertent thermal retinal damage.[9,10,17,18,22]

This study has significant limitations including obtaining data by retrospective chart review, small size, short duration, lack of controls, and description of a novel treatment technique used by only two surgeons. However, the results are consistent between the two reporting clinical centers and consistent with the findings of all previous reports of SDM for DME, including randomized clinical trials. By virtue of its safety profile, SDM seems uniquely suited to the treatment of FIDME, as well as preventative treatment before the development of visual loss or measurable foveal thickening. We believe that further study of the potential for new early interventions such as SDM to optimize DME management is warranted.

Key words: transfoveal, micropulse, laser, diabetes, diabetic macular edema, safety, early treatment.

Acknowledgments

The authors thank Leslie M. Nizole, MS, and David C. Musch, PhD, MPH, of the University of Michigan School of Medicine, Department of Biostatistics, for their assistance in editing the article and statistical data analysis.

References

1. Centers for Disease Control. Available at: www.cdc.gov/diabetes/news/docs/dpp.htm. Accessed March 25, 2013.
2. Early Treatment of Diabetic Retinopathy Study. Photocoagulation for diabetic macular edema. ETDRS report no. 4. Int Ophthalmol Clin 1987;27:265–272.
3. Nguyen QD, Brown DM, Boyer DS, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012;119:789–801.
4. Early Treatment of Diabetic Retinopathy Study. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. ETDRS report no. 2. Ophthalmology 1987;94:761–774.
5. Paulus YM, Jain A, Nomoto H, et al. Selective retinal therapy with microsecond exposures using a continuous line scanning laser. Retina 2011;31:380–388.
6. Moorman CM, Hamilton AM. Clinical applications of the micro-pulse diode laser. Eye (Lond) 1999;13:145–150.
7. Laursen ML, Moeller F, Sander B, et al. Subthreshold micropulse diode laser treatment in diabetic macular oedema. Br J Ophthalmol 2004;88:1173–1179.
8. Figueira J, Khan J, Nunes S, et al. Prospective randomised controlled trial comparing sub-threshold micropulse diode laser photocoagulation and conventional green laser for clinically significant diabetic macular oedema. Br J Ophthalmol 2009;93:1341–1344.
9. 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.
10. 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.
11. 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.
12. Veritti D, Giullio A, Lanzetta P. Drug safety evaluation of intravitreal triamcinolone acetonide. Expert Opin Drug Saf 2012;11:331–340.
13. Do VD, Nguyen QD, Khwaja AA, Channa C. Ranibizumab for edema of the macula in diabetes study. 3-year outcomes and the need for prolonged frequent treatment. JAMA Ophthalmol 2013;131:139–145.
14. Smiddy WE. Economic considerations of macular edema therapies. Ophthalmology 2011;118:1827–1833.
15. Lanzetta P, Van Nuys K, Irwin T, Gallagher M. The Economic Burden of Diabetic Macular Edema from a U.S. Private Payor Perspective. Annual meeting of the Association for Research in Vision and Ophthalmology, Vancouver, Canada, 2011. IVOS annual meeting program abstract 5532.
16. Moshfegi AA, Rosenfeld PJ, Flynn HW, Schwartz SG. Endophthalmitis after intravitreal injection of vascular endothelial growth factor antagonists. Six year experience at a university referral center. Retina 2011;31:662–668.
17. 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.
18. 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.
19. Wolf-Shnurrbusch UEK, Ceklic L, Brinkmann CK, et al. Macular thickness measurements in healthy eyes using six different optical coherence tomography instruments. Invest Ophthalmol Vis Sci 2009;50:3432–3437.
20. Dhamdhere KP, Bearse MA Jr, Harrison W, et al. Associations between local retinal thickness and function in early diabetes. Invest Ophthalmol Vis Sci 2012;53:6122–6128.
21. Panda-Jonas S, Jonas JB, Jakobczyk-Zmila M. Retinal pigment epithelial cell count, distribution, and correlations in normal eyes. Am J Ophthalmol 1996;121:181–189.
22. Dorin G. Subthreshold and micropulse photocoagulation. Semin Ophthalmol 2003;18:147–153.
23. Sinclair SH, Mainster MA. Introduction diabetic macular edema: Pathogenics, Treatment. Seminars in Ophthalmology 1999;14:197–219.
24. Sinclair SH, Alaniz R, Presti P. Laser treatment of diabetic macular edema: comparison of ETDRS-level treatment with threshold-level treatment by using high-contrast discriminant central visual field testing. Semin Ophthalmol 1999;14:214–222.
25. Morgan CM, Schatz H. Atrophic creep of the retinal pigment epithelium after focal macular photocoagulation. Ophthalmology 1989;96:96–103.
26. Venkatesh P, Ramanjulu R, Azad R, et al. Subthreshold micropulse diode laser and double frequency neodymium:YAG laser in treatment of diabetic macular edema: a prospective, randomized study using multifocal electroretinography. Photomed Laser Surg 2011;29:727–733.
27. Aktan-Yavuz GY, Bekiroglu UN, Presti P, Sinclair SH. Central field perimetry of discriminated targets: I. Results for normal individuals using high-contrast targets. Eye (Lond) 2009;23:2082–2089.