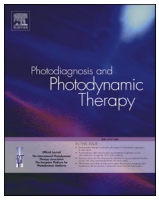
Photodiagnosis and Photodynamic Therapy 51 (2025) 104430

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt



Research Paper

Comparison of one-year real-world outcomes between red (670 nm) subthreshold micropulse laser treatment and intravitreal aflibercept injection for treatment-naïve diabetic macular edema

Wataru Kikushima *, Yukiko Furuhata, Taiyo Shijo, Mizuki Matsumoto, Yoichi Sakurada, Daphne Viel Tsuru, Kenji Kashiwagi

Department of Ophthalmology, University of Yamanashi, Shimokato 1110, Chuo, Yamanashi Prefecture, Japan

ARTICLE INFO

Keywords:
Treatment-naïve DME
Red SMPL
Anti-VEGF agent
aflibercept, OCTA

ABSTRACT

Purpose: To evaluate the treatment outcomes of subthreshold micropulse laser (SMPL) with a wavelength of 670 nm (red) for treatment-naïve diabetic macular edema (DME).
Methods: A retrospective observational study which included 42 eyes in 34 patients diagnosed with treatment-naïve DME was conducted. Twenty-one eyes underwent red SMPL and the other 21 eyes underwent intravitreal injection of aflibercept (IVA) as initial treatment and were followed up for 12 months. Best-corrected visual acuity (BCVA), central retinal thickness (CRT) on optical coherence tomography (OCT), vessel density (VD), and foveal avascular zone area on OCT angiography (OCTA) were measured and compared between the two groups.
Results: In the red SMPL group, the mean BCVA slightly improved from 0.29 ± 0.28 at baseline to 0.22 ± 0.29 at 12 months ($p = 0.18$), while the mean CRT significantly decreased from 472 ± 200 μm at baseline to 320 ± 136 μm at 12 months ($p = 0.003$). At 12 months from baseline, the mean change in BCVA and CRT were similar between the red SMPL and IVA groups ($p = 0.79$ and $p = 0.31$, respectively). No significant change was detected in OCTA parameters except for VD at the nasal section in the red SMPL group.
Conclusion: Red SMPL for treatment-naïve DME maintained BCVA and significantly reduced CRT at 12 months. These treatment outcomes were equivalent to IVA in real-world settings, which tend to be inferior to clinical trials.

1. Introduction

Diabetic retinopathy (DR) is one of the possible severe complications of diabetes mellitus (DM)[1,2]. If left untreated, it can progress to proliferative DR (PDR) which may lead to severe and irreversible vision loss secondary to tractional retinal detachment or neovascular glaucoma. In addition, diabetic macular edema (DME) is also a major vision-threatening pathology which can occur in any severity of DR among patients with DM[3].

Diabetic retinopathy and DME are characterized by the following mechanisms: High blood sugar levels affect blood vessels in the eye, which start to leak, and new leaky blood vessels may grow, leading to DR and finally DME. Diabetic macular edema implies retinal thickening caused by the accumulation of intraretinal fluid, mainly in the inner and outer plexiform layers of the retina due to the hyperpermeability of the retinal vasculature. Complaints of blurry vision or dark spots can lead to the discovery of DME at any stage of DR (mild, moderate, or severe non-proliferative DR or proliferative DR) [4]. About 1 in 15 diabetic patients develop DME [2]. The disease is often established via investigations including the Amsler grid, optical coherence tomography (OCT), or fluorescein angiography.

At present, intravitreal injection of an anti-vascular endothelial growth factor (VEGF) agent is the first-line therapy for DME[5–8]. However, repeated injections are sometimes required for recurrent disease leading to consequent financial and physical burden on patients[9,10]. In randomized controlled trials of DME, the mean best-corrected visual acuity (BCVA) gains of 6–13 Early Treatment Diabetic Retinopathy Study (ETDRS) letters were achieved with approximately 7–12 intravitreal anti-VEGF injections during the first year of the treatment [7,8,11,12]. The number of injections was reported to be smaller in the following years, however, most patients were required to continue injections to maintain their vision.

* Corresponding author.
E-mail address: wkikushima@yamanashi.ac.jp (W. Kikushima).

https://doi.org/10.1016/j.pdpdt.2024.104430
Received 1 October 2024; Received in revised form 11 November 2024; Accepted 2 December 2024
Available online 5 December 2024

Several therapies for DME are available as an alternative for anti-VEGF intravitreal injections such as focal/grid laser, sub-tenon triamcinolone acetonide injection, intravitreal dexamethasone, and pars plana vitrectomy[13–16]. Among these treatment options, the subthreshold micropulse laser treatment (SMPL), characterized by its 'spotless' and low-risk laser procedure, has been widely utilized in the recent decade[17–23]. Compared to the conventional photocoagulation which burns the leaky sites with a continuous wave laser, SMPL affects the tissue by giving the energy as a low-intensity and short-duration pulse, allowing the tissue to rest (cooling) between pulses. SMPL is reported to target the retinal pigment epithelium (RPE) and activate its pump function without damaging photoreceptors. It has been also reported that SMPL induces heat shock protein activation, leading to repair and recovery processes of RPE function. In addition, SMPL is reported to be effective in DME regression by modifying Muller cells, which are involved in retinal fluid control and inflammatory response [24]. Favorable efficiency of SMPL using 810 nm (infrared) or 577 nm (yellow) wavelengths for DME has been reported in previous studies [25–27]. In contrast, there is not as many studies which support the use of the 670 nm (red) wavelength for DME. We previously compared the efficacy and safety of red and yellow SMPLs for DME and reported equivalent visual and morphological outcomes[28]. However, the study included eyes with previously treated DMEs in 70 % of participants. In the present study, we aimed to evaluate the efficacy and safety of red SMPL for the treatment naïve DME and compare those with anti-VEGF agents.

2. Methods

A retrospective review of patient medical charts with treatment-naïve DME treated at the ophthalmology department of the University of Yamanashi Hospital between April 2017 and March 2023 was conducted. This study was approved by the University of Yamanashi Hospital Institutional Review Board (approval number 2089) and abided by the Tenets of the Declaration of Helsinki.

During the first visit, informed consent for the treatment was obtained from all participants. The inclusion criteria were as follows: (1) patients with treatment-naïve DME with a foveal thickness $>$ 300 μm, (2) patients treated with red SMPL or intravitreal aflibercept injection (IVA) as an initial therapy and were followed up every two months, and (3) patients who completed 12 months of follow-up. The exclusion criteria were as follows: (1) patients with untreated proliferative DR or severe non-proliferative DR (since these patients were prioritized to undergo vitrectomy or pan-retinal photocoagulation), (2) patients with macular edema (ME) caused by other ocular pathologies such as retinal vein occlusion, age-related macular degeneration, macular telangiectasia, or high myopia, (3) patients with other ocular pathology that might affect the central visual field including cataract, severe glaucoma, optic neuritis, macular hole, or epiretinal membrane, (4) vitrectomized eyes, and (5) patients with systemic disorders that might affect the central retinal thickness (CRT) such as renal failure, heart failure, or hemodialysis.

At the initial visit, all patients underwent comprehensive ophthalmic examination which included visual acuity, intraocular pressure measurement using a Goldmann applanation tonometer, slit-lamp biomicroscopy, dilated pupil fundoscopy using a 90D non-contact lens, and dilated pupil indirect ophthalmoscopy. The patients also underwent multimodal imaging which included color fundus photography (CFP), spectral-domain OCT (SD-OCT)/OCT angiography (OCTA) examination, fundus autofluorescence (FAF). Fluorescein angiography was also performed at baseline to determine the severity of DR. All of these measurements were performed under pupil dilation. The baseline parameters including the latest serum hemoglobin A1c (HbA1c) level and the duration of DM were extracted from the medical questionnaire. Patients were divided into two groups according to the initial treatment regimen: the red SMPL group, and the IVA group.

2.1. Optical coherence tomography angiography

All OCTA images were recorded using HS-100 OCT (Canon Lifecare Solutions, Kanagawa, Japan). Each patient underwent OCTA scans of the central 3 × 3 mm area at each follow-up period. Each OCTA scan was automatically segmented into the superficial capillary plexus (SCP), deep capillary plexus (DCP), and choriocapillary plexus (CCP) slabs using the built-in imaging software. OCTA images at each visit were recorded three times and averaged for the analyses. To evaluate the OCTA parameters precisely, we referred to the previous studies and excluded OCTA images with a quality index lower than 4/10 from the study [29,30].

As OCTA parameters, vessel density (VD) and the foveal avascular zone (FAZ) size were analyzed. Each OCTA image was binarized using a modified version of the previously reported method by the built-in software to measure OCTA parameters [31]. Briefly, after processing with a top-hat filter, the OCTA image was duplicated and different binarization methods were performed on each image. One image was processed by a Hessian filter and was binarized using average thresholding. The other image was processed by a Sobel filter and unsharp mask filter. Then the processed image was binarized using median local thresholding. Finally, the 2 different binarized images were combined to generate the final binarized image in which only pixels that existed on both binarized images were included. VD was recorded as the proportion of vessel area with blood flow over the 3 mm diameter range from the central fovea, described as the inner circle of the Early Treatment Diabetic Retinopathy Study (ETDRS) grid. The inner circle of ETDRS was divided into 5 subfield areas including the fovea, superior, inferior, temporal, and nasal subfields. The border of each FAZ was manually detected from the SCP slabs of OCTA images and then FAZ size was measured using the built-in software.

2.2. Subthreshold micropulse laser treatment

In the red SMPL group, patients underwent SMPL with a wavelength of 670 nm as an initial treatment. All SMPLs were performed using a TruScan Laser (LIGHTMED, San Clemente, CA, USA). The settings of the red SMPL were as follows: wavelength of 670 nm, spot size of 200 μm, 5 % duty cycle of 200 msec, and fixed laser power of 400 mW. The number of spots depended on the extension of DME. A test shot was performed on the retina outside of the arcade vessels. Most of the eyes showed no visible fleck at the time of the test burn outside of the macula. If a visible fleck by the test burn was detected, we carefully and gradually reduced laser power until the spot became invisible, put the first SMPL at the corner of the treated area, and again confirmed that no visible fleck appeared. After determining the appropriate laser power, SMPL was applied repeatedly and continuously to cover the entire area of DME except for the foveola with zero-spot spacing.

After the initial SMPL at baseline, the patients were followed up every two months. If the CRT was $>$300 μm or there was no improvement in BCVA on follow-up, retreatment of SMPL using the same settings as the initial treatment was performed. If the CRT was $>$500 μm or the BCVA deterioration was $>$0.2 logMAR (equivalent to 10 letters in ETDRS charts), rescue treatment with IVA was allowed based on the judgement of the retinal specialists.

Though the procedure of SMPL has been proven to be free from adverse events because of its noninvasive laser power, the possible adverse effect includes an overtreatment by a medical error and subsequent damage to RPE or outer retina [21]. To evaluate the safety of the procedure, the patients underwent FAF examination at 6 and 12 months from baseline. Each FAF image was assessed to confirm that no laser scarring by SMPL was detected.

2.3. Anti-VEGF treatment

In the IVA group, patients underwent IVA (aflibercept 2mg/0.05 ml)

as an initial treatment and were followed up every two months. If residual or recurrent exudation was detected on SD-OCT, the patients received additional IVAs (as-needed IVA) during the follow-up period.

2.4. Statistical analysis

All statistical analyses were conducted using the StatFlex ver. 7 software (Arctec Co., Ltd., Osaka, Japan). BCVA was measured on a decimal scale and was converted into a logMAR for statistical analyses. The differences in the categorical and the continuous variables between the two groups were tested by the chi-square test and the Mann-Whitney U test. The significance of differences between the variables before and after the treatment was tested using the paired-*t*-test.

The primary outcome measures were BCVA improvement and CRT reduction at 12 months from baseline. The mean change of the OCTA parameters was also compared between the two groups.

3. Results

Twenty-one eyes in 18 patients in the red SMPL group and 21 eyes in 16 patients in the IVA group were included in the present study. The mean age was 65.5 ± 9.3 years and 23 patients (67.6 %) were male. The mean baseline BCVA was 0.34 ± 0.28 and the mean CRT on SD-OCT was 478 ± 167 μm. Table 1 shows the baseline demographic characteristics of the two groups. There was no significant difference in age, sex, serum HbA1c level, duration of DM, DR severity, baseline BCVA, and baseline CRT between the two groups. A representative case treated with the red SMPL is shown in Fig. 1.

3.1. Mean change in BCVA

Fig. 2 illustrates the mean change in BCVA during the follow-up period in the red SMPL and the IVA groups. In the red SMPL group, mean BCVA slightly improved from 0.29 ± 0.28 at baseline to 0.22 ± 0.29 at 12 months, however, the difference was insignificant ($p = 0.18$). In the IVA group, mean BCVA significantly improved initially at 2 to 4 months from baseline, however, the significance disappeared thereafter. The final BCVA was similar to that at baseline (0.38 ± 0.29 vs. 0.34 ± 0.28, $p = 0.41$). There was no significant difference in the BCVA improvement between the two groups at 12 months ($p = 0.79$).

3.2. Mean change in CRT on SD-OCT

Fig. 3 shows the mean change in CRT during the follow-up period in the two groups. In the red SMPL group, the mean CRT significantly decreased from 472 ± 200 μm at baseline to 320 ± 136 μm at 12 months ($p = 0.003$, Fig. 3A). Similarly, the mean CRT in the IVA group significantly decreased from 485 ± 131 μm at baseline to 394 ± 178 μm at 12 months ($p = 0.02$, Fig. 3A). There was no significant difference in the CRT reduction between the two groups at 12 months ($p = 0.31$, Fig. 3B).

Table 1
Baseline demographic characteristics of patients in the red SMPL and the IVA groups.

	Red SMPL ($n = 21$)	IVA ($n = 21$)	P Value
Age	67.6 ± 9.1	63.4 ± 9.1	0.09
Sex (F/M)	6/15	8/13	0.51
HbA1c (%)	7.0 ± 0.9	8.1 ± 2.5	0.29
DM duration (months)	93±99	135±116	0.39
DR severity			0.26
Mild NPDR	6 (28.6 %)	3 (14.3 %)	
Moderate NPDR	15 (71.4 %)	18 (85.7 %)	
Severe NPDR	0	0	
PDR	0	0	
Mean logMAR BCVA	0.29±0.28	0.38±0.29	0.26
Mean CRT on SD-OCT (μm)	472±200	485±131	0.35

BCVA: best-corrected visual acuity, CRT: central retinal thickness, DM: diabetes mellitus, DR: diabetic retinopathy, HbA1c: hemoglobin A1c, IVA: intravitreal aflibercept injection, logMAR: logarithm of the minimal angle of resolution, NPDR: non-proliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy, SD-OCT: spectral-domain optical coherence tomography.

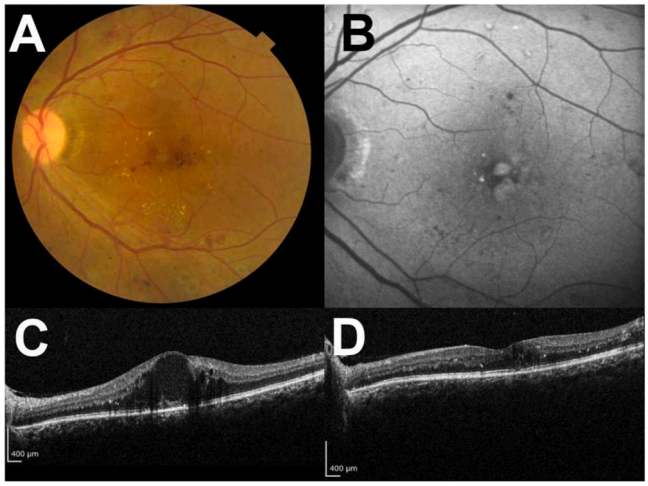


Fig. 1. A 57-year-old male with diabetic macular edema (DME) in the left eye treated by red subthreshold micropulse laser (SMPL). (A) Color fundus photography of the left eye at baseline shows center-involving DME surrounded by hard exudates and dot hemorrhages. Best-corrected visual acuity (BCVA) in the left eye was 0.22 logMAR. He received red SMPLs four times in 12 months of follow-up. (B) Fundus autofluorescence of the left eye at 12 months reveals no visible laser spot on the macula. Hyperfluorescent lesions in the fovea indicate intraretinal cysts. (C) A horizontal spectral-domain optical coherence tomography (SD-OCT) scan at baseline shows cystoid DME. The central retinal thickness (CRT) was 673 μm. (D) A horizontal SD-OCT scan at 12 months from baseline reveals significant absorption of edema. The CRT drastically reduced to 262 μm. His BCVA in the left eye improved to −0.08 logMAR.

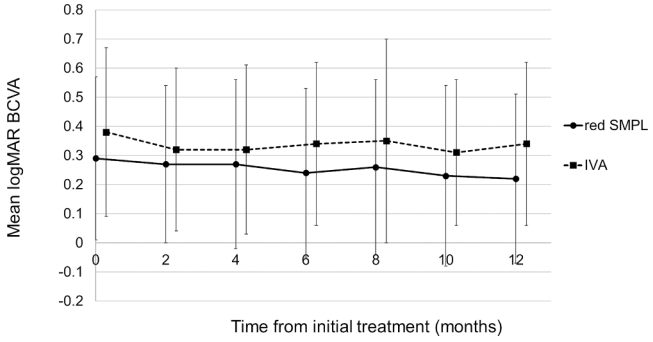


Fig. 2. The mean change in best-corrected visual acuity (BCVA) during the follow-up period in the red SMPL and the IVA groups. In the red SMPL group, mean BCVA slightly improved from 0.29 ± 0.28 at baseline to 0.22 ± 0.29 at 12 months, however the difference was insignificant ($p = 0.18$). In the IVA group, mean BCVA significantly improved at 2 to 4 months from baseline but the significance disappeared thereafter. The final BCVA was equivalent to that at baseline (0.38 ± 0.29 vs. 0.34 ± 0.28, $p = 0.41$).

3.3. Mean change in OCTA parameters

Table 2 demonstrates the mean change in OCTA parameters in the red SMPL and the IVA groups. In the red SMPL group, VD in the SCP and DCP slab at the nasal section significantly increased at 12 months from baseline ($p = 0.021$ and $p = 0.044$, respectively). In the IVA group, VD in the CCP slab at the central and the nasal sections significantly increased at 12 months from baseline ($p = 0.033$ and $p = 0.048$, respectively). FAZ area showed no significant change in both groups.

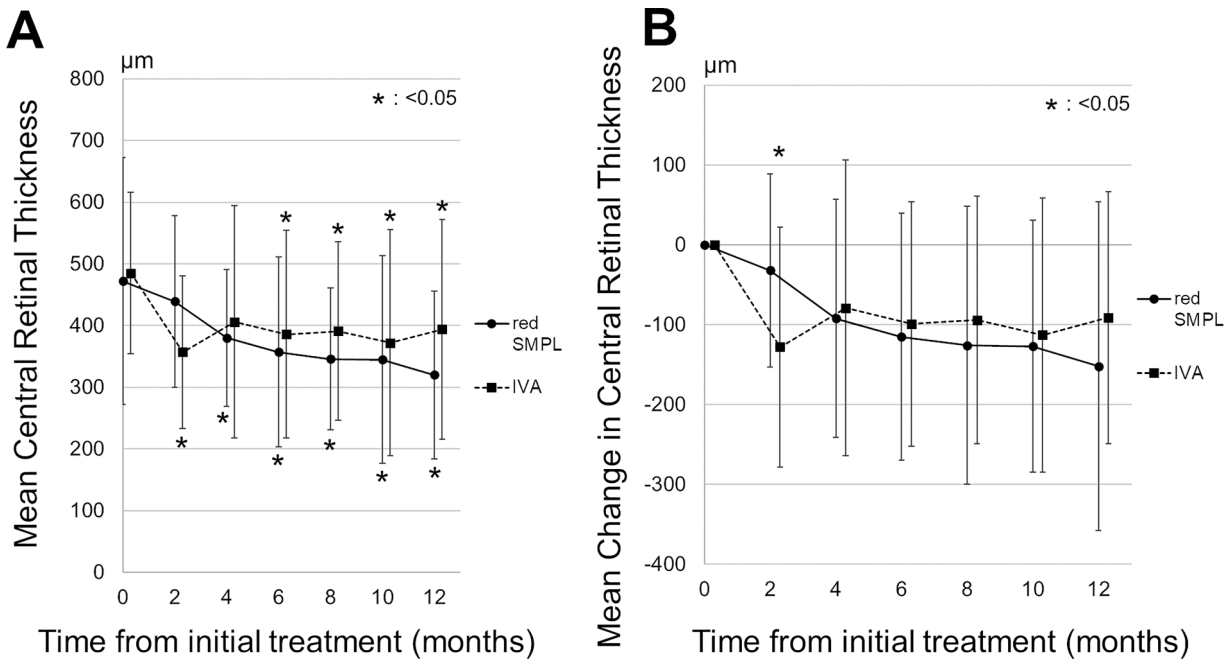


Fig. 3. The mean change in central retinal thickness (CRT) during the follow-up period in the red SMPL and the IVA groups. (A) In the red SMPL group, the mean CRT significantly decreased from 472 ± 200 μm at baseline to 320 ± 136 μm at 12 months ($p = 0.003$). Similarly, the mean CRT in the IVA group significantly decreased from 485 ± 131 μm at baseline to 394 ± 178 μm at 12 months ($p = 0.02$). (B) The mean CRT reduction between the two groups. At 2 months, the mean CRT reduction in the IVA group was greater than the red SMPL groups ($p = 0.03$). However, the significance disappeared at 4 months, and the CRT reduction at 12 months between the two groups was equivalent ($p = 0.31$).

3.4. Number of additional treatments and safety assessments

In the red SMPL group, the mean number of additional SMPLs was 4.8 ± 1.4 during the follow-up period. Two eyes (9.5 %) received IVAs twice as rescue treatments. Among these eyes, one eye showed BCVA deterioration > 0.2 logMAR (from 0.15 at baseline to 0.4 at months 4 and 10) and the rescue IVAs were performed. The BCVA improved to 0.15 logMAR at month 12 and the rescue IVA was discontinued. Another eye showed CRT thicker than 500 μm at months 2 and 10. After the rescue IVAs were performed, the CRT was reduced and the rescue IVA was discontinued. In the IVA group, the mean number of additional IVAs was 3.6 ± 1.4 during the follow-up period. There was no significant difference in the number of additional treatments between the two groups ($p = 0.08$).

During the follow-up period, no adverse events were recorded in both groups. Patients in the red SMPL group were examined using FAF at 6 and 12 months and no hypofluorescent lesion was detected in the treated area (Fig. 1).

4. Discussion

The present study investigated the treatment efficacy and safety of red SMPL for DME and compared those with IVA, the currently standard treatment for DME. Patients in the red SMPL group maintained their BCVA and showed a significant reduction in CRT during the 12 months of follow-up. The visual and anatomical outcomes of the red SMPL group were similar to those of the as-needed IVA group. To the best of our knowledge, this is the first study which reported the therapeutic potential of red SMPL for treatment-naïve DME. As mentioned, we previously compared the treatment outcomes between red and yellow SMPLs, but the study included 70 % of eyes with already previously treated DME.

In the literature, the favorable treatment outcomes of SMPL with the wavelength of 810 nm (infrared) and 577 nm (yellow) have been reported. Vujosevic *et al*. compared the treatment outcomes of the infrared and yellow SMPLs for mild DME (CRT < 400 μm)[32]. They reported that the mean BCVA was stable, and the mean CRT significantly reduced during 6 months of follow-up in both treatment modalities. Recently, Lois and colleagues (DIAMONDS Study Group) compared the treatment efficacy and safety of yellow SMPL with standard laser treatment (SL) for DME in a large randomized clinical trial[33]. The mean BCVA change from baseline to month 24 was −2.43 ± 8.20 letters in the SMPL group and −0.45 ± 6.72 letters in the SL group ($p = 0.046$). They concluded that SMPL showed equivalent treatment efficacy and safety to SL, requiring slightly higher number of laser treatments. Similar to previous studies, the mean BCVA change was −0.07 ± 0.25 logMAR and the mean CRA reduction was -152 ± 206 μm in the red SMPL group. However, despite the significant reduction in CRT, the BCVA improvement did not achieve statistical significance in the red SMPL group. We considered that the amount of CRT reduction might have been insufficient to yield a significant BCVA improvement. In the study by Sadda et al., the duration and amount of residual DME after anti-VEGF therapy were reported to be negatively correlated with long-term visual outcomes[34]. In our current study, the mean CRT at 12 months was still 320 ± 136 μm in the red SMPL group hence DME did not completely disappear and persisted in most patients. Thus, we attribute this insignificant visual improvement in the red SMPL group to the residual DME. Furthermore, our study included eyes with DME which were 400 μm or thicker, whereas many previous studies included DMEs of 400 μm or thinner. Considering that CRT thinner than 250 μm has been reported to be associated with the BCVA improvement[34], the red SMPL would be more suitable for mild DME with CRT thinner than 400 μm.

Several studies reported changes seen in OCTA after treatment for DR or DME[30]. Vujosevic et al. reported that the FAZ area in the DCP and the area of cysts in the SCP and DCP significantly decreased at 6 months after yellow SMPL[35]. They also reported a significant decrease in the number of microaneurysms (MA) in the SCP and DCP at 6 months in the treated eyes only. However, no significant change in VD was detected in their study. Recently, Li et al. compared the efficacy of conventional laser and SMPL for DME and assessed changes in OCTA parameters and reported statistically significant changes in all OCTA metrics, including VD, vessel length density, and fractal dimension in

Table 2
Comparison of optical coherence tomography angiography parameters in the red SMPL and IVA groups.

	Red SMPL		P Value	IVA		P Value
	Baseline	Month 12		Baseline	Month 12	
Vessel Density (%)						
SCPc	23.1 ± 8.9	23.7 ± 7.4	0.74	23.1 ± 8.7	27.2 ± 4.4	0.07
SCPu	36.2 ± 8.8	36.3 ± 8.2	0.88	32.9 ± 9.6	36.7 ± 4.4	0.08
SCPl	35.4 ± 7.7	36.1 ± 6.2	0.54	32.0 ± 11.7	35.0 ± 4.8	0.14
SCPt	34.0 ± 9.7	35.1 ± 9.5	0.44	32.0 ± 12.0	35.3 ± 5.2	0.23
SCPn	33.6 ± 8.8	36.8 ± 5.4	0.021	32.9 ± 11.5	37.3 ± 3.7	0.10
DCPc	24.1 ± 13.0	24.5 ± 11.7	0.86	24.4 ± 10.6	27.5 ± 9.0	0.29
DCPu	35.8 ± 12.2	36.6 ± 10.3	0.57	33.4 ± 14.0	36.5 ± 10.1	0.29
DCPl	35.2 ± 11.0	35.8 ± 11.2	0.79	31.7 ± 14.4	33.6 ± 10.0	0.41
DCPt	33.4 ± 13.6	35.3 ± 12.8	0.31	33.8 ± 14.3	35.8 ± 8.1	0.55
DCPn	33.3 ± 13.6	37.3 ± 9.5	0.044	31.9 ± 15.7	36.4 ± 9.7	0.19
CCPc	42.0 ± 7.0	42.1 ± 6.0	0.93	35.4 ± 12.3	41.2 ± 4.0	0.033
CCPu	42.7 ± 4.9	41.8 ± 4.0	0.27	38.3 ± 8.8	41.3 ± 4.7	0.07
CCPl	41.5 ± 4.5	41.9 ± 4.3	0.68	38.4 ± 7.3	41.1 ± 3.3	0.08
CCPt	41.6 ± 8.5	41.9 ± 8.1	0.70	37.9 ± 8.6	41.1 ± 3.7	0.15
CCPn	40.7 ± 5.0	43.4 ± 2.2	0.055	37.8 ± 9.7	42.4 ± 3.9	0.048
FAZ area (mm^2)	0.41 ±0.16	0.39 ±0.16	0.33	0.34 ±0.17	0.35 ±0.13	0.68

CCP: choriocapillary plexus, DCP: deep capillary plexus, FAZ: foveal avascular zone, IVA: intravitreal aflibercept injection, SCP: superficial capillary plexus, SMPL: subthreshold micropulse laser, c: central circle, u: upper section, l: lower section, t: temporal section, n: nasal section.

the DCP and CCP for both groups[36]. In contrast, our current findings did not detect a significant change in OCTA parameters except for VD at the nasal section in the red SMPL group. We consider that the small number of patients might have influenced the results. Further research with a large cohort is necessary to elucidate the effect of SMPL on retinal perfusion and vascular construction in patients with DME.

Nakao *et al.* previously reported that the visual outcomes of anti-VEGF treatment for DME in real-world settings tended to be inferior to those reported in clinical trials[37]. In a prospective multicenter study, Sugimoto et al. reported that the total number of IVAs for DME over 24 months was 3.6 ± 3.0 injections and BCVA was maintained in real-world settings[38]. They concluded that the patients in the real-world setting received fewer injections than those in the clinical trials, suggesting that a margin for improvement exists in clinical practice. Similarly in this study, patients in the IVA group received 3.6 ± 1.4 additional injections and did not achieve a significant improvement in BCVA at 12 months. We consider that the undertreatment of IVA in this real-world setting might have led to fewer improvements in BCVA than those observed in clinical trials.

Recently, different groups have been trying to evaluate the treatment outcomes of the combination of SMPL and anti-VEGF injections for DME. In the meta-analysis, Hosoya et al. reported that adding SMPL to anti-VEGF therapy could significantly reduce the number of injections compared to anti-VEGF monotherapy while achieving similar BCVA and CRT. Ma et al. also reported in the other meta-analysis that combining SMPL with anti-VEGF injections might reduce the total number of injections required, improve BCVA, and reduce CRT at 12 months. In addition, Peroni et al. investigated the new procedure of combined laser, short pulse grid and SMPL, plus intravitreal ranibizumab for DME. They reported that the combination therapy achieved significant improvement in BCVA and CRT at 12 months with a mean number of 8.29 injections and 3.67 SMPLs. These findings encourage the utilization of SMPL with the conventional treatment for DME.

There are several limitations in this study. Firstly, the study is retrospective in nature with a relatively small number of participants. Secondly, the optimal laser settings for the red SMPL have not yet been established. Though we chose a fixed laser power of 400 mW, the titration of laser power might be more appropriate for determining threshold power. In addition, the mean number of additional red SMPLs in this study was 4.8 ± 1.4 during the follow-up period, which means most of the patients needed repeated lasers every 2 months. To improve visual outcomes and reduce the number of treatments, the most effective settings of SMPL including laser power, duty cycle, and wavelength remain to be determined. Thirdly, the evaluation of OCT/OCTA parameters did not include some parameters which were previously reported to correlate with visual outcomes, including disorganization of retinal inner layers, disruption of the external limiting membrane, location and amount of fluid, fluctuation in CRT, and change in MA. The fourth limitation was that we did not include smoking history and body mass index, which might affect the OCTA parameters. The fifth limitation was that we could not follow up on the change in HbA1c values, which might affect the treatment outcomes.

In conclusion, this is the first study to evaluate the efficacy of the red SMPL in the treatment naïve DME. As a result, the red SMPL maintained BCVA and significantly reduced CRT at 12 months. These treatment outcomes were equivalent to IVA in real-world settings, which tend to be inferior to clinical trials.

CRediT authorship contribution statement

Wataru Kikushima: Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yukiko Furuhata:** Resources, Data curation. **Taiyo Shijo:** Resources, Data curation. **Mizuki Matsumoto:** Resources, Data curation. **Yoichi Sakurada:** Writing – review & editing, Supervision. **Daphne Viel Tsuru:** Writing – review & editing. **Kenji Kashiwagi:** Supervision.

References

[1] N. Cheung, P. Mitchell, T.Y. Wong, Diabetic retinopathy, Lancet 376 (9735) (2010) 124–136, https://doi.org/10.1016/s0140-6736(09)62124-3. Jul 10.
[2] J.W. Yau, S.L. Rogers, R. Kawasaki, et al., Global prevalence and major risk factors of diabetic retinopathy, Diabetes Care 35 (3) (2012) 556–564, https://doi.org/10.2337/dc11-1909. Mar.
[3] A. Kume, K. Kashiwagi, Recent epidemiological status of ocular and other major complications related to diabetes mellitus in Japan, Ophthalmologica 243 (6) (2020) 404–412, https://doi.org/10.1159/000506747.
[4] T.H. Fung, B. Patel, E.G. Wilmot, W.M. Amoaku, Diabetic retinopathy for the non-ophthalmologist, Clin. Med. (Lond) 22 (2) (2022) 112–116, https://doi.org/10.7861/clinmed.2021-0792. Mar.
[5] T. Hirano, Y. Toriyama, Y. Takamura, et al., Outcomes of a 2-year treat-and-extend regimen with aflibercept for diabetic macular edema, Sci. Rep. 11 (1) (2021) 4488, https://doi.org/10.1038/s41598-021-83811-y. Feb 24.
[6] J.F. Payne, C.C. Wykoff, W.L. Clark, et al., Long-term outcomes of treat-and-extend ranibizumab with and without navigated laser for diabetic macular oedema: TREX-DME 3-year results, Br. J. Ophthalmol. 105 (2) (2021) 253–257, https://doi.org/10.1136/bjophthalmol-2020-316176. Feb.
[7] C.C. Wykoff, J.G. Garweg, C. Regillo, et al., KESTREL and KITE Phase 3 Studies: 100-Week Results With Brolucizumab in Patients With Diabetic Macular Edema, Am. J. Ophthalmol. 260 (2024) 70–83, https://doi.org/10.1016/j.ajo.2023.07.012. Apr.
[8] T.Y. Wong, Z. Haskova, K. Asik, et al., Faricimab treat-and-extend for diabetic macular edema: two-year results from the randomized phase 3 yosemite and rhine trials, Ophthalmology. 131 (6) (2024) 708–723, https://doi.org/10.1016/j.ophtha.2023.12.026. Jun.

[9] M. Sugimoto, H. Tsukitome, F. Okamoto, et al., Clinical preferences and trends of anti-vascular endothelial growth factor treatments for diabetic macular edema in Japan, J. Diabetes. Investig. 10 (2) (2019) 475–483, https://doi.org/10.1111/jdi.12929. Mar.
[10] Z.L. Teo, Y.C. Tham, M. Yu, et al., Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis, Ophthalmology. 128 (11) (2021) 1580–1591, https://doi.org/10.1016/j.ophtha.2021.04.027. Nov.
[11] Q.D. Nguyen, D.M. Brown, D.M. Marcus, et al., Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE, Ophthalmology. 119 (4) (2012) 789–801, https://doi.org/10.1016/j.ophtha.2011.12.039. Apr.
[12] J.S. Heier, J.F. Korobelnik, D.M. Brown, et al., Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies, Ophthalmology. 123 (11) (2016) 2376–2385, https://doi.org/10.1016/j.ophtha.2016.07.032. Nov.
[13] Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group, Arch. Ophthalmol. 103 (12) (1985) 1796–1806. Dec.
[14] H.P. Qi, S. Bi, S.Q. Wei, et al., Intravitreal versus subtenon triamcinolone acetonide injection for diabetic macular edema: a systematic review and meta-analysis, Curr. Eye Res. 37 (12) (2012) 1136–1147, https://doi.org/10.3109/02713683.2012.705412. Dec.
[15] H. Imai, A. Tetsumoto, H. Yamada, et al., Long-term effect of cystotomy with or without the fibrinogen clot removal for refractory cystoid macular edema secondary to diabetic retinopathy, Retina 41 (4) (2021) 844–851, https://doi.org/10.1097/IAE.0000000000002921. Apr 1.
[16] D.S. Boyer, Y.H. Yoon, R. Belfort Jr., et al., Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema, Ophthalmology. 121 (10) (2014) 1904–1914, https://doi.org/10.1016/j.ophtha.2014.04.024. Oct.
[17] Y. Takatsuna, S. Yamamoto, Y. Nakamura, et al., Long-term therapeutic efficacy of the subthreshold micropulse diode laser photocoagulation for diabetic macular edema, Jpn. J. Ophthalmol. 55 (4) (2011) 365–369, https://doi.org/10.1007/s10384-011-0033-3. Jul.
[18] J.K. Luttrull, G. Dorin, Subthreshold diode micropulse laser photocoagulation (SDM) as invisible retinal phototherapy for diabetic macular edema: a review, Curr. Diabetes. Rev. 8 (4) (2012) 274–284, https://doi.org/10.2174/157339912800840523. Jul 1.
[19] D.B. Chang, J.K. Luttrull, Comparison of subthreshold 577 and 810 nm micropulse laser effects on heat-shock protein activation kinetics: implications for treatment efficacy and safety, Transl. Vis. Sci. Technol. 9 (5) (2020) 23, https://doi.org/10.1167/tvst.9.5.23. Apr.
[20] L. Frizziero, A. Calciati, G. Midena, et al., Subthreshold micropulse laser modulates retinal neuroinflammatory biomarkers in diabetic macular edema, J. Clin. Med. 10 (14) (Jul 15 2021), https://doi.org/10.3390/jcm10143134.
[21] B. Sabal, S. Teper, E. Wylęgała, Subthreshold micropulse laser for diabetic macular edema: a review, J Clin Med. 12 (1) (2022), https://doi.org/10.3390/jcm12010274. Dec 29.
[22] J.H. Mei, Z. Lin, Subthreshold micropulse diode laser treatment in diabetic macular edema: biological impact, therapeutic effects, and safety, Int. Ophthalmol. 44 (1) (2024) 3, https://doi.org/10.1007/s10792-024-02973-6. Feb 3.
[23] M. Yamamoto, Y. Miura, K. Hirayama, et al., Predictive factors of outcome of selective retina therapy for diabetic macular edema, Int. Ophthalmol. 40 (5) (2020) 1221–1232, https://doi.org/10.1007/s10792-020-01288-6. May.
[24] Ç. Bildirici, M. Ozturk, F. Önder, Six-month results of 577 nm subthreshold micropulse laser therapy in non-center involving diabetic macular edema, Photodiagnosis. Photodyn. Ther. 47 (2024) 104084, https://doi.org/10.1016/j.pdpdt.2024.104084. Jun.
[25] L. Frizziero, A. Calciati, T. Torresin, et al., Diabetic macular edema treated with 577-nm subthreshold micropulse laser: a real-life, long-term study, J. Pers. Med. 11 (5) (2021), https://doi.org/10.3390/jpm11050405. May 13,.
[26] R.M. Passos, F.K. Malerbi, M. Rocha, et al., Real-life outcomes of subthreshold laser therapy for diabetic macular edema, Int. J. Retina Vitreous. 7 (1) (2021) 4, https://doi.org/10.1186/s40942-020-00268-3. Jan 9.
[27] M. Zavorkova, J. Nekolova, L. Prochazkova, et al., Diabetic macular edema treatment with subthreshold micropulse laser - five-year long monitoring, Biomed. Pap. Med. Fac. Univ. Palacky. Olomouc. Czech. Repub. 167 (1) (2023) 74–79, https://doi.org/10.5507/bp.2022.055. Mar.
[28] W. Kikushima, T. Shijo, Y. Furuhata, et al., Comparison of the 1-year visual and anatomical outcomes between subthreshold red (670 nm) and yellow (577 nm) micro-pulse laser treatment for diabetic macular edema, Pharmaceuticals. (Basel) 14 (11) (2021), https://doi.org/10.3390/ph14111100. Oct 28.
[29] M. Al-Sheikh, K. Ghasemi Falavarjani, H. Akil, S.R Sadda, Impact of image quality on OCT angiography based quantitative measurements, Int. J. Retina Vitreous. 3 (2017) 13, https://doi.org/10.1186/s40942-017-0068-9.
[30] N.K. Waheed, R.B. Rosen, Y. Jia, et al., Optical coherence tomography angiography in diabetic retinopathy, Prog. Retin. Eye Res. 97 (2023) 101206, https://doi.org/10.1016/j.preteyeres.2023.101206. Nov.
[31] A. Uji, S. Balasubramanian, J. Lei, et al., Impact of multiple en face image averaging on quantitative assessment from optical coherence tomography angiography images, Ophthalmology. 124 (7) (2017) 944–952, https://doi.org/10.1016/j.ophtha.2017.02.006. Jul.
[32] S. Vujosevic, F. Martini, E. Longhin, et al., Subthreshold Micropulse yellow laser versus subthreshold micropulse infrared laser in center-involving diabetic macular edema: morphologic and functional safety, Retina 35 (8) (2015) 1594–1603, https://doi.org/10.1097/IAE.0000000000000521. Aug.
[33] N. Lois, C. Campbell, N. Waugh, et al., Diabetic macular edema and diode subthreshold micropulse laser: a randomized double-masked noninferiority clinical trial, Ophthalmology. 130 (1) (2023) 14–27, https://doi.org/10.1016/j.ophtha.2022.08.012. Jan.
[34] S.R. Sadda, J. Campbell, P.U. Dugel, et al., Relationship between duration and extent of oedema and visual acuity outcome with ranibizumab in diabetic macular oedema: a post hoc analysis of Protocol I data, Eye (Lond) 34 (3) (2020) 480–490, https://doi.org/10.1038/s41433-019-0522-z. Mar.
[35] S. Vujosevic, C. Toma, E. Villani, et al., Subthreshold micropulse laser in diabetic macular edema: 1-year improvement in OCT/OCT-angiography biomarkers, Transl Vis Sci Technol. 9 (10) (2020) 31, https://doi.org/10.1167/tvst.9.10.31. Sep.
[36] G. Li, M. Ho, S. Li, et al., Comparing functional and vascular layer outcomes of laser photocoagulation versus subthreshold micropulse laser for diabetic macular edema: an oct-angiography study, Retina 43 (5) (2023) 823–831, https://doi.org/10.1097/iae.0000000000003711. May 1,.
[37] S. Nakao, S. Kusuhara, T. Murakami, Anti-VEGF therapy for the long-term management of diabetic macular edema: a treat-to-target strategy based on macular morphology, Graefes. Arch. Clin. Exp. Ophthalmol. (2024), https://doi.org/10.1007/s00417-024-06558-y. Jul 12.
[38] M. Sugimoto, C. Handa, K. Hirano, et al., Intravitreal aflibercept for diabetic macular edema in real-world clinical practice in Japan: 24-month outcomes, Graefes. Arch. Clin. Exp. Ophthalmol. 260 (11) (2022) 3489–3498, https://doi.org/10.1007/s00417-022-05703-9. Nov.