Diabetic macular edema treatment with subthreshold micropulse laser – five-year long monitoring

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Aim. The objective of this study was to evaluate the efficacy of diabetic macular edema (DME) therapy using subthreshold micropulse laser (SMPL) with a wavelength of 577 nm during a long-term monitoring period of 5 years.
Methods. The cohort included the total number of 52 eyes of 34 patients with DME. All underwent the standard laser treatment for the diabetic retinopathy outside the macula and DME treatment with SMPL. Subsequent check-ups were followed every 3 months in the first year of treatment, and every 4 to 6 months in the following years. The treatment was combined neither with focal macular laser nor with anti-VEGF therapy.
Results. The mean central retinal thickness (CRT) was 345.9 µm SD 122.6 µm at the beginning of the monitoring. At the end of the follow-up period five years after treatment it was 256.4 µm SD 98.4 µm. The mean CRT decreased by 89.5 µm SD 153.6 µm during 5 years. At the beginning of the monitoring, before treatment with SMPL, the best corrected visual acuity (BCVA) was 70.0, SD 10.1 ETDRS letters. One year after therapy, BCVA was 72, SD 10.0 letters, two years later it was 71.4, SD 10.4 letters and decreased to 66.9, SD 12.1 letters after 5 years. The mean BCVA decreased by merely 3.1, SD 10.9 letters during 5 years.
Conclusion. Based on our long-term observations, the DME treatment with SMPL appears to be an effective method for reducing DME and protecting BCVA against rapid worsening.

Key words: diabetic macular edema, subthreshold micropulse laser therapy

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INTRODUCTION

Diabetic retinopathy (DR) is a typical microvascular complication of diabetes mellitus (DM). Its emergence is related to specific morphological changes which result from metabolic disorders in patients with DM. The incidence of DM is continuously rising[1]. DR is the fifth most common cause of preventable blindness, and it is a highly frequent cause of moderate and subsequently significant visual impairment. The most common manifestation of DR that reduces vision is diabetic macular edema (DME). A clinically significant diabetic macular edema (CSME) occurs in 6–10% of DM patients[2]. Local ophthalmological treatment options for CSME are laser photocoagulation (FC) (ref.[3-6]), intravitreal application of vascular growth factor blockers (anti-VEGF) or corticosteroids, and then surgical treatment, performance of pars plana vitrectomy (PPV). In the Czech Republic, anti-VEGF therapy is limited by the reimbursement conditions applied by health insurance companies (i.e. glycated haemoglobin maximum 70 mmol/mol and the duration of DME of maximum 2 years), and therefore this therapy is not available to all patients. The optimal treatment scheme for DME must be modified according to the patient's general condition, the ophthalmological findings, as well as his/her motivation and compliance[7,8].

Laser treatment for DME is performed using the conventional FC, which causes scars on the retina. Depending on the type of DME, grid or focal FC is performed. Another option is applying a subthreshold micropulse laser (SMPL) to the macula. This treatment does not scar the retina; no scar is detectable by any method at the time of the treatment or later[9]; and the treatment can be repeated as needed. The efficacy of the therapy is monitored via the development of central retinal thickness (CRT) and via the development of the best corrected visual acuity (BCVA). OCT shows a noticeable reduction of CRT and retreat of intraretinal cysts. The efficacy of SMPL therapeutic mechanism may be due to a possible anti-inflammatory effect of SMPL through the improvement of retinal glial cells metabolism/activity[10,11]. SMPL may also suppress retinal edema by aquaporin 3 upregulation, which might have improved retinal edema by drainage of subretinal fluid[12].

The most significant clinical risk factors for the progression of DR disease are: duration of DM disease, arterial hypertension and hyperglycemia, body habitus (obesity type), variability of blood pulsation changes

(pulse wave analysis). The risk of DR is also increased by a number of other factors, e.g. profession, smoking, dyslipidemia and obesity. More recently, the impact of the systemic inflammatory response related to DR has been researched[13-15].

The objective of the study was to evaluate the efficacy of DME therapy using SMPL with a wavelength of 577 nm over a long-term monitoring period of 5 years. Such long-term results have not been published yet.

Key question

If SMPL is applied, is it possible to achieve and maintain long-term reduction of DME and improvement or at least maintenance of the initial BCVA?

COHORT AND METHODS

The cohort consisted of patients with DR complicated by DME; the duration of DME was not decisive. None of the patients met the reimbursement criteria for DME treatment with intravitreal administration of anti-VEGF or did not wish to undergo that treatment. The decisive criterion for the patients to be included in the cohort was the existence of non-ischemic cystoid edema in the macula with or without foveal involvement (i.e. patients with the CRT lower than 250 μm and with a vision of 85 letters of ETDRS (Early Treatment Diabetic Retinopathy Study) optotype or less were included). The exclusion criteria were previous DME treatment with anti-VEGF therapy and PPV, and another concomitating macular disease, opacification of the optic media, or other eye diseases affecting visual acuity (VA).

The cohort consisted of 52 eyes of 34 patients. Data are presented as means, standard deviations (SD), medians (m) and minimums (min.) with maximums (max.) The mean age was 61 years; SD = 10.9; m = 61.5 (min. 28, max. 80). The average duration of DM was 14.8 years; the SD = 8.7; m = 1 (min. 0.5, max. 34). 4 patients suffered from DM of the 1st type, 30 patients suffered from the DM of the 2nd type. The average value of glycated hemoglobin (HbA1c) was 66.1 mmol/mol SD = 14.4, m = 67.5 (min. 32, max. 99) at the beginning of the study and changed to 69.6 mmol/mol SD = 14.5, m = 67.5 (min. 34, max. 102) in the 1st year, 72.2 mmol/mol SD = 18.2, m = 71 (min. 37, max. 121) in the 2nd year, 67.5 mmol/mol SD = 15.3, m = 65 (min. 41, max. 103) in the 3rd year, 68.9 mmol/mol SD = 16.5, m = 66 (min. 40, max. 105) in the 4th year, 66.2 mmol/mol SD = 15.2, m = 67 (min. 38, max. 99) in the 5th year. However, there was a great variability in the SD of the cohort, ranging from 14.4 to 18.2 mmol/mol over the years; the minimum value was 32 mmol/mol and the maximum value was 124 mmol/mol. Based on the verbal description in the documentation, the duration of DME was 2.6 years; SD = 3.4, m = 1 (min. 0, max. 16). The verification of DME based on OCT was maximally 1 year before being included in the study. Non-proliferative DR was diagnosed in 48 eyes (2 cases of the incipient stage, 11 cases of the moderate stage, 35 case of the severe stage), in 4 eyes there was an incipient proliferative DR. DME was focal in 35 eyes, and a combination of focal and diffuse DME occurred in 17 eyes.

All the patients signed an informed consent with retinal FC treatment and were informed about all available methods of DME treatment. This is a safe and standard treatment for DME (ref.[16-18]), therefore the approval by the ethics commission was not required.

At the beginning of the study, the following examinations were performed: BCVA was measured with a standardized method using ETDRS optotypes from 20 feet. Standard ophthalmological examination using slit lamp and biomicroscopic retinal examinations were performed. Examinations of retina was done by optical coherence tomography (OCT) using the SPECTRALIS® Tracking Laser Tomography by Heidelberg Engineering.

Before being included in the study research, all the patients underwent treatment of the retina outside the macula with a standard laser pulse therapy using the VISULAS Trion Carl Zeiss® device. The treatment depended on the type of DR, and, if needed, it was supplemented during the research period. On the day of being included in the study, all participants underwent DME treatment with a MicroPulse yellow diode laser of IQ 577™ IRIDEX® brand with a wavelength of 577 nm. We used the Ocular Goldmann Three Mirror Lens for both the types of laser (this lens has magnification of 0.93x). A MicroPulse 5% duty cycle laser beam mode was used to treat the macula. This means that with the total exposure of 200 ms, the effective laser dose was divided into 100 micro pulses, the total length of which was 5%, i.e. 10 ms. During the first two years, the recommendations by the laser manufacturer were followed and power dosing was carried out in the area nasal to the papilla using a continuous laser mode with the path of 100 μm in diameter, the time of 100 ms and the initial power of 50 mW. Gradually, the power was increased up to the level at which a visible mark was left on the retina. Then, the setting was made for the MicroPulse mode 5% duty cycle, for the exposure of 200 ms and for the power 2–3 times bigger than that measured during dosing. Subsequently, the dosing was changed according to the recommendations made by Oxford Eye Clinic[19]. The laser was still in the MicroPulse mode. The 200 μm laser spot was aimed at the area of the retina around the macula in which there was no edema. We started with a low power of 500 mW, and gradually the power was increased by 50 mW until a laser burn was visible. In the Caucasian-type population, which is dominant in our region, a laser burn can be seen when the power between 800 and 1400 mW is used. Then this individual threshold dose was reduced by 50% and used for MicroPulse treatment (the resulting power is between 400 and 700 mW). The threshold dose is determined separately for each eye. During the monitoring, the threshold dose is repeatedly remeasured and modified during further check-ups (the height of the DME and media opacification play their roles). In all participants the foveal area was avoided during SMPL. SMPL was performed using a 3 x 3 spot "pattern" laser mode. The spots were always placed tightly next to each other (high density) (ref.[20]).

BCVA and OCT examinations were performed at each subsequent check-up. Subsequent check-ups were followed every 3 months in the first year of the treatment, and every 4 to 6 months in the following years. The overall monitoring period was 5 years. The FC treatment of the retina was repeated during the check-ups as needed. The indication for repeating the SMPL is the occurrence of cystoid edema in the macula. Thus, if the DME finding improved, the SMPL was not performed at each check-up. The frequency of repeated FC therapy was also observed. The treatment was combined neither with focal macular laser nor with anti-VEGF therapy.

Statistical analysis

Data are presented as means, standard deviations, medians, minimums with maximums. Wilcoxon's Signed-Rank test with Holm-Bonferroni modification tested difference of follow up parameters against beginning. Spearman Correlation was used as a measure of linear relationship. Calculations were made by Statistical software NCSS 2021 Statistical Software (2021). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss. The level of statistical significance was set to α=0.05.

RESULTS

At the beginning of the monitoring period, the mean CRT was 345.9 μm. One year later, the mean CRT was 317.2 μm, CRT improved or stabilized in 28 eyes (54%) and CRT deteriorated in 24 eyes (46%) and the mean CRT changed by -28.7 μm. Two years later, the mean CRT was 310.8 μm, CRT improved or stabilized in 29 eyes (56%) and CRT deteriorated in 23 eyes (44%) and the mean CRT changed by -35.0 μm. Three years later, the mean CRT was 295.7 μm, CRT improved or stabilized in 34 eyes (65%) and CRT deteriorated in 18 eyes (35%) and the mean CRT changed by -50.7 μm. Four years later, the mean CRT was 266.5 μm, CRT improved or stabilized in 39 eyes (75%) and CRT deteriorated in 13 eyes (25%) and the mean CRT changed by -79.4 μm. Five years later, the mean CRT was 256.4 μm, CRT improved or stabilized in 43 eyes (83%) and CRT deteriorated in 9 eyes (17%). After 5-year long monitoring, the mean CRT changed by -89.5 μm, SD = 153.6 μm, m = -61.5 μm (min. -571 μm, max. 268 μm) (see Table 1 and Fig. 1).

At the beginning of monitoring, BCVA was 70 ETDRS letters. After one year, BCVA was 72.6 ETDRS letters, BCVA improved by more than 5 letters in 10 eyes (19%), BCVA was more or less stabilized (i.e. improvement or deterioration of 5 letters or less) in 39 eyes (75%), BCVA decreased by more than 5 letters in 3 eyes (6%), the mean BCVA changed by +2.6 ETDRS letters. After 2 years, BCVA was 71.4 ETDRS letters, BCVA improved by more than 5 letters in 12 eyes (23%), BCVA was stabilized in 30 eyes (58%), BCVA decreased by more than 5 letters in 10 eyes (19%), the mean BCVA changed by +1.4 ETDRS letters. After 3 years, BCVA was 69.7 ETDRS letters, BCVA improved by more than 5 letters in 9 eyes (17%), BCVA was stabilized in 29 eyes (56%), BCVA decreased by more than 5 letters in 14 eyes (27%) the mean BCVA changed by -0.3 ETDRS letters. After 4 years, BCVA was 68.7 ETDRS letters, BCVA improved by more than 5 letters in 12 eyes (23%), BCVA was stabilized in 23 eyes (44%), BCVA decreased by more than 5 letters in 17 eyes (33%) the mean BCVA changed by -1.3 ETDRS letters. After 5 years, BCVA was 66.9 ETDRS letters, SD 12.1, m = 69 (min. 42, max. 85). After this 5-year-long monitoring, BCVA was more or less stabilized (i.e. improvement or deterioration of 5 letters or less) in 24 eyes (46%); BCVA improved by more than 5 letters in 9 eyes (17%), out of which 4 eyes (8%) improved by at least 3 ETDRS lines (15 letters and more); BCVA decreased by more than 5 letters in 19 eyes (37%), out of which 7 eyes (13%) deteriorated by more than 3 ETDRS lines. In total, BCVA improved or stabilized in 33 eyes (63%). After 5-year-long monitoring, the mean BCVA decreased by 3.1 ETDRS letters, SD = 10.9 (min. -30, max. 20) (see Table 2 and Fig. 2).

The frequency of repeated SMPL therapy was in total, over 5 years, 9.4 laser treatments of the macula on average; SD = 3.4 m = 10 (min. 2, max. 14). In the first year, SMPL treatment was performed 3.7 times on average SD = 0.6, m = 4 (min. 2, max. 4), in the 2nd year it was 2.3 times on average SD = 1.0, m = 3 (min. 0, max. 3), in the 3rd year it was done 1.6 times SD = 1.1, m = 2 (min. 0, max. 3), in the 4th year it was 1.1 times SD = 0.9, m = 1.5 (min. 0, max. 2), and in the 5th year, the treatment was performed 0.8 times on average SD = 0.8, m = 1 (min. 0, max. 2).

There was no correlation between the number of SMPL recurrences over 5 years and baseline HbA1c (Spearman coefficient was r = 0.0789) or baseline CRT (Spearman coefficient was r = 0.0602).

No correlation was found between baseline HbA1c and change of CRT after 5 years (Spearman coefficient r = 0.186). No significant correlation of CRT change with HbA1c change in individual years was found (Spearmann coefficient was in 1st year r = 0.4271, in 2nd year r = 0.0107, in 3th year r = 0.2574, in 4th year r = 0.0414 and in the 5th year r = 0.0645).

There were no early or long-term complications of the SMPL method in our series.

DISCUSSION

The literature describes various methods of SMPL dosing; fixed or variable treatment regimen are applied[5,18]. Study Donati et al.[21] compares fixed SMPL (F-SMPL) and variable treatment regimen of SMPL (V-SMPL). Fixed SMPL (F-SMPL) was performed with the following parameters: 100 μm spot size on slit lamp, 5% duty cycle of 0.2 s, and 250 mW power. To choose the power of the variable treatment regimen of SMPL (V-SMPL) group, continuous laser power was titrated to a barely visible burn and then switched to MicroPulse mode, multiplying the test burn power by 4 and using a 5% duty cycle of 0.2 s. CRT reduced more in V-SMPL at 6 and 12 months. F-SMPL appears more suitable minimizing treatment time and reducing the possible errors due to wrong titra-

Table 1. Central retinal thickness (CRT) (μm), 5-year long monitoring and evaluation of the change CRT from the beginning.

Year	CRT (μm) Mean	SD	Median	Min.	Max.	Mean change	*P*	Statistically significant No modification	Statistically significant Holm-Bonferroni modification
0	345.9	122.6	314	168	760	–	–		
1	317.2	104.1	277	115	559	−28.7	0.29867	No	No
2	310.8	101.3	280.5	107	534	−35.0	0.15712	No	No
3	295.7	115.0	260.5	99	590	−50.7	0.00575	*P*<0.01	*P*<0.05
4	266.5	101.3	242	71	542	−79.4	0.00008	*P*<0.001	*P*<0.001
5	256.4	98.4	224	99	526	−89.5	0.00001	*P*<0.001	*P*<0.001

Table 2. Best corrected visual acuity (BCVA) (ETDRS letters), 5-year long monitoring and evaluation of the change BCVA from the beginning.

Year	BCVA (ETDRS letters) Mean	SD	Median	Min.	Max.	Mean change	*P*	Statistically significant No modification	Statistically significant Holm-Bonferroni modification
0	70.0	10.1	71.5	35	85	–	–		
1	72.6	10.0	75	43	85	2.6	0.00240	*P*<0.01	*P*<0.05
2	71.4	10.4	74	41	85	1.4	0.24008	No	No
3	69.7	11.5	69.5	42	85	−0.3	0.71715	No	No
4	68.7	12.5	68.5	28	85	−1.3	0.81303	No	No
5	66.9	12.1	69	42	85	−3.1	0.95486	No	No

Table 3. Our results of DME treatment with SMPL compared with the alredy published studies in the monitoring period 12 months.

Study	n	Difference BCVA at 12 months (mean ± SD) logMAR (ETDRS letters)	Difference CRT at 12 months (mean ± SD) μm	F-SMPL/ V-SMPL	Ref.
This study	52	−0.05 ± 0.12 (+2.6 ± 7.0)	−28.7 ± 153.8	V	
Vujosevic et al. (2010)	32	+0.02 ± 0.18 (−1 ± 9.0)	−46.6 ± 73.5	F	22
Luttrull et al. (2014)	39	−0.03 ± 0.11 (+1.5 ± 5.5)	−23.3 ± 64.1	F	23
Vesela et al. (2018)	21	+0.002 (-0.1)	−67	V	24
Akkaya et al. (2019)	37	−0.042 (+2.1)	−39.08 ± 46.84	V	25
Vujosevic et al. (2020)	37	−0.132 0.168 (+6.6 ± 8.4)	−10.46	F	10
Donati et al. (2020)	15	−0.008 (+0.4)	−45.46	V	21
	24	+0.017 (-0.85)	−33.8	F	21

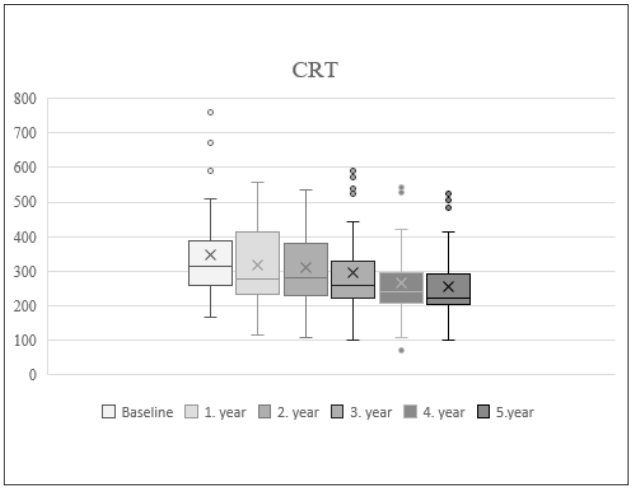

Fig. 1. Box-plots showing central retinal thickness (CRT) (μm), 5-year long monitoring.

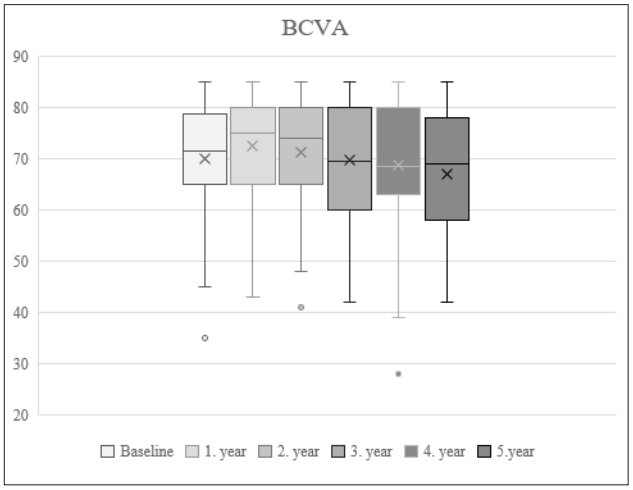

Fig. 2. Box-plots showing best corrected visual acuity (BCVA) (ETDRS letters), 5-year long monitoring.

tion in the switch from continuous to MicroPulse mode. Our dosing of SMPL was variable from the beginning. We changed the original titration method, which uses switching between continuous and MicroPulse mode, to the method recommended by Oxford Eye Clinic[19]. This method was preferred for its speed, safety and efficacy. Furthermore, there is no switching between continuous and MicroPulse mode and the dosing of laser radiation is individualized. The aim of our research was not to determine which of the SMPL dose titration methods is better. That is why the change in dosing made during check-ups in later years is not considered to be important.

In our research, SMPL was avoided in the fovea area for the safety of the treatment, and for excluding a possibility of scar formation.

Our results of DME treatment with SMPL can be compared with the published results only in case of the monitoring period up to 12 months (see Table 3). Data related to longer monitoring periods have not been published. The results of the research studies carried out after a treatment period longer than 1 year differ due to the difference in entry criteria and due the used SMPL dosing. The entry criteria were in the study by Vujosevic et al. (2010) (ref.[22]) CRT at least 250 μm, BCVA at least 35 letters, in the study by Luttrull et al. (2014) (ref.[23]) the presence of a foveaincluding DME and BCVA of at least 70 letters, in the study by Vesela et al. (2018) (ref.[24]) the presence of DME, in the study by Akkaya et al. (2019) (ref.[25]) presence of DME and BCVA of at least 78 letters, in the study of Vujosevic et al. (2020) (ref.[10]) presence of DME and CRT maximum 400 μm, BCVA minimum 78 letters or less than 78 letters patients who refused or could not have treatment with anti-VEGF intravitreal injection, in the study of Donati et al. (2020) (ref.[21]) CRT less than 400 μm and BCVA at least 35 letters. In this study, the entry criterion was the presence of DME. The change in BCVA after 12 months varies between -1 and +6.6 letters in the cited studies, in this study there was an improvement in average BCVA of +2.6 letters after 12 months. The change in CRT was -10.4 μm to -67 μm in the cited studies, in this study the reduction in CRT after 12 months was -28.7 μm. Our results are comparable to the results of other studies carried out after the first year of treatment.

A slight non statistically significant deterioration of BCVA with a continuing statistically significant (P<0.001) improvement in CRT were found in our cohort after 5 years of monitoring. During the monitoring period, there were fluctuations in DM compensation depending on the patients´ compliance (HbA1c in the range of 32 to 124 mmol/mol, mean SD HbA1c over 5 years was 15,25 mmol/mol), on associated acute diseases or worsened chronic diseases and on the overall stress level. 30 (88%) of 34 patients had HbA1c fluctuation (transient deterioration) of 15 mmol/mol or more during the 5-year follow-up. Only 14 eyes (27%) of 11 patients (32%) had an interannual variation (deterioration) CRT of more than 100 μm (median SD CRT over 5 years was 102.7 μm) during 5 years. After 5 years, worsening of more than 100 μm from baseline persisted in only 3 (6%) eyes of 2 patients (6%). CRT changes over the years depend on many factors, GlykHb fluctuations alone did not always lead to CRT worsening in our cohort. Together with these factors, the DME finding changed as well.

The long-term persistence of DME then led in some cases to a functional deterioration of the findings, and thus to a decrease in BCVA. After 5 years, CRT improved in 83% of the eyes, and the mean reduction in CRT by 89.5 μm occurred. BCVA improved or stabilized in 63% of the eyes. Therefore, the long-term maintenance of BCVA stability and the deterioration of the mean BCVA by 3.1 ETDRS letters after 5 years can be considered to be acceptable.

SMPL appears to be a suitable method not only for monotherapy, as it is the case of our study research, but it also appears to be advantageous for combination with antiVEGF intraocular injections. Numerous studies show that the use of SMPL in the treatment of DME reduces the number of needed antiVEGF injections[26,27].

CONCLUSIONS

In our cohort of eyes with DME, a statistically significant improvement in the mean CRT was reached after five years of monitoring and SMPL macular treatment. The mean BCVA statistically significantly improved during the first year after SMPL. Until the fifth year of the monitoring period, the change in the median BCVA was statistically insignificant. In the fifth year after treatment, there was a deterioration of only 3 ETDRS letters compared to the initial value. Based on our long-term monitoring, the DME treatment with SMPL appears to be an effective method. Its main advantage is that no scarring occurs on the retina, and therefore it can be repeated as needed or it can be combined with other kinds of treatment.

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