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ORIGINAL ARTICLE

Management of cystoid macular edema secondary to retinitis pigmentosa via subliminal micropulse yellow laser

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Abstract

To investigate the effects of subliminal micropulse yellow laser application on the central macular thickness and best-corrected visual acuity in cystoid macular edema secondary to retinitis pigmentosa patients. This prospective open-label clinical trial, conducted between January 2018 and October 2019, included 32 eyes of 29 patients who had cystoid macular edema secondary to retinitis pigmentosa. Patients were treated by subliminal micropulse yellow laser for one session. Central macular thickness and best-corrected visual acuity changes were investigated just before the treatment and 1 year later after the one session of the treatment. The mean central macular thickness was 651.3 μm before the treatment and 247.7 μm at 12 months after the treatment. The decrease in mean central macular thickness was statistically significant ($p = 0.01$). Median best-corrected visual acuity was 66.8 ETDRS letters before the treatment and 70.0 letters at 12 months after the treatment. The increase in best-corrected visual acuity was not statistically significant ($p = 0.18$). Eighty-six percent of the patients stated that the quality of central vision increased and that color vision, contrast sensitivity, and distortion improved. We did not encounter any serious adverse events related to the application of subliminal micropulse yellow laser. The subliminal micropulse yellow laser seems to be a therapeutic, effective, and safe option for the treatment of non-inflammatory and resistant cystoid macular edema secondary to retinitis pigmentosa patients. ClinicalTrials.gov ID: NCT04234438, January 17, 2020.

Keywords Retinitis pigmentosa · Cystoid macular edema · Intraretinal cysts · Subliminal micropulse laser

Introduction

Retinitis pigmentosa (RP) is a progressive photoreceptor and retinal pigment epithelial (RPE) degeneration that begins with night vision loss, resulting in narrowing of the visual field and legal blindness. RP is a heterogeneous genetic disorder, affecting 1/3000–8000 people worldwide [1, 2]. RP is the result of a mutation in one of more than 260 genes. These genes are responsible for the synthesis of peptides involved in the visual cycle. These genes are also responsible for the synthesis of growth factors responsible for the conversion of glucose to adenosine triphosphate (ATP) or responsible for the removal of metabolic wastes [3, 4].

The incidence of cystoid macular edema (CME) in RP has been reported to be between 10 and 50% [5, 6]. There are several hypotheses about the pathogenesis of cystoid macular edema in RP. The first hypothesis is explained by Müller cell hypertrophy and its paracrine effects [7–9]. Mutations in the retinal pigment epithelium disrupt the synthesis of some growth factors. Stress caused by apoptosis in rod cells in the periphery leads to the ectopic synaptogenesis of the central Müller cells. Müller cells undergo compensatory hypertrophy and synthesize excessive growth factors [10–12]. This paracrine effect provides protection of the central vision. Edema at a certain level is considered to be protective of photoreceptors and should not be treated [13–15]. However, if edema is excessive and prolonged, it leads to a break in synaptic connections in the neural retina and an increase in neurodegeneration. CME also deteriorates central visual quality in patients with impaired peripheral vision [7, 8]. Treatment should be considered only if the edema is excessive and disrupts central vision or in the presence of inflammation. According to our clinical experience, when the central macular thickness exceeds 500 μm, the central visual quality of the patients decreases and requires treatment.

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Other pathophysiological causes of CME in RP are explained by low-grade inflammation and retinal autoantibodies [8, 16]. In some genetic mutation types of RP, such as the X-linked RPGR gene mutation, vitritis, lipofuscin deposits, and inflammation are predominant. Ciliopathy leads to inflammation and CME, which increases the photoreceptor loss rate [17–20]. Immediate treatment of inflammation-induced edema can slow disease progression. Inflammatory edema appears as cystoid macular edema similar to the petal, whereas compensatory edema due to Müller cell hypertrophy is seen as separated intraretinal cysts [7, 8, 21]. Inflammatory edema can respond well to carbonic anhydrase inhibitors, while compensatory edema does not [22, 23].

The results of the treatment of CME in RP are controversial because the compensatory or inflammatory distinction is not clear. Treatments such as oral or topical carbonic anhydrase inhibitors, intravitreal anti-vascular endothelial growth factor or corticosteroid injections, grid laser applications, and pars plana vitrectomy might be effective in some cases with CME secondary to RP [22–27]. Most of these treatments have either insufficient response or excessive side effects.

To our knowledge, so far, we have not found a scientific publication about the use of micropulse yellow laser for treatment cystoid macular edema secondary to retinitis pigmentosa.

Subliminal micropulse laser (SL-MPL) is a method developed for the treatment of macular diseases. Subthreshold short pulses prevent thermal damage. The coagulation scars do not form with SL-MPL treatment. Subletally induced RPE cells lead to the release of some restorative growth factors (GFs) and suppression of some inflammatory cytokines such as pigment epithelium-derived factor (PEDF) and vascular endothelial growth factor (VEGF) inhibitors [28–33].

The purpose of this study was to investigate the effect of 577 nm yellow SL-MPL application on central macular thickness (CMT) and on best-corrected visual acuity (BCVA) in patients with non-inflammatory, resistant cystoid macular edema secondary to retinitis pigmentosa.

Materials and methods

This prospective open-label clinical trial was conducted at the Bioretina Clinic Ankara/TURKEY. The study included 32 eyes of 29 patients who had CME secondary to RP. RP patients with various degrees of BCVA and narrowed visual field were studied between January 2018 and October 2019. The diagnosis of RP was based on clinical history, fundus appearance, genetic test, full-field electroretinogram (ERG), and/or multifocal ERG findings. The diagnosis of CME and CMT measurement was based on optical coherence tomography (OCT) (RTVue XR "Avanti," Optovue, Fremont, CA, USA). All patients enrolled in this study underwent a complete routine ophthalmic examination with the ETDRS chart (Topcon CC 100 XP, Japan) used to measure visual acuity.

Subjects

Inclusion criteria:

- Diagnosis of any phenotypic variation of RP
- Presence of separated intraretinal cysts
- Central macular thickness of ≥ 500 μm
- Unresponsive to systemic or topical carbonic anhydrase inhibitors
- No interventional treatment for macular edema in the last 3 months

Exclusion criteria:

- Patients with signs of inflammation, such as cells in the vitreous, intraretinal white dots, septa-free similar to the petal edema.
- Patients responding to systemic or topical carbonic anhydrase inhibitors.
- Any interventional treatment has been applied for macular edema in the last 3 months.
- The presence of other causes that may lead to CME, such as contractile epiretinal membrane with epicenters, uveitis, vitreous traction, or diabetes.

CMT and BCVA were recorded before and at each control during the 12 months following SL-MPL application. CMT was measured using the manual segmentation program of the OCT device.

SL-MPL was applied one session to patients with a 577 nm yellow laser (EasyRet, Quantel Medical, Cedex, France). Laser application was performed with a Mainster Standard contact laser lens (Volk Optical, Mentor, OH, USA) after pupil dilation and topical anesthesia. To determine the appropriate personalized calibration value, the single-spot test shot was applied under the green filter to a non-edematous and outside temporal vascular arcade. The power was set at 50% to form a barely visible laser spot. The laser parameters used were 160 μm spot diameter, 200 ms duration, 5% operating cycle, and zero spacing with 5 × 5 pattern shape. SL-MPL was applied to the areas where edema was detected in OCT and examination. Laser spots were applied after creating a clear round target light on the edematous area. During application, foveola was protected.

Time frame

The patients were checked on the 1st day, 1st week, 1st month, 2nd month, 3rd month, 6th month, and 12th month after SL-MPL application. The time frames recorded were as follows:

- Before application: A period of 3 months prior to the SL-MPL application. In this period, cases not responding to systemic and topical carbonic anhydrase inhibitors were detected.
- 0 (baseline): Just before the SL-MPL application.
- 1: 1st month after SL-MPL application.
- 2: 2nd month after SL-MPL application.
- 3: 3rd month after SL-MPL application.
- 4: 6th month after SL-MPL application.
- 5: 12th month after SL-MPL application.

Primary outcome measure

Central macular thickness (CMT) (time frame: 0, 1, 2, 3, 4, and 5). This was measured manually from the internal limiting membrane to the Bruch membrane in the center of the fovea. The CMT values obtained from the baseline testing and the final examination were analyzed and compared to determine effectiveness.

Secondary outcome measures

Best-corrected visual acuity (BCVA) (time frame: 0, 1, 2, 3, 4, and 5). BCVA is the number of ETDRS letters that the patient can read after the best correction. The visual acuity scores obtained from the baseline testing and the final examination were analyzed and compared statistically to determine effectiveness.

Definition of safety outcome

Macular burn, ellipsoid zone destruction, vision loss, macular hemorrhages, and vitreoretinal interface alterations were considered to be serious adverse ocular events.

Statistical analysis

The statistical comparisons were made primarily between the baseline and final values from the same eye. A paired *t* test was used for comparison of baseline and final results in the same group. The difference between CMT and BCVA before and 12 months after the SL-MPL application was compared. In this study, *p* values smaller than 0.05 were considered statistically significant. Analyses were carried out with SPSS for Windows (v22; IBM Corp.; Armonk, NY, USA).

Results

In this study, 32 eyes belonging to 29 RP patients were included. Of the 29 patients, 13 were male, and 16 were female; their median age was 38.8 years (range, 18–67 years). Thirty-two eyes were applied to SL-MPL.

The mean central macular thickness was 651.3 μm before treatment and 247.7 μm at 12 months after treatment. The decrease in CMT was detected at 2 months after the SL-MPL application in all cases. CMT values were stable in the 12th month and the same as the 2nd month in all cases. The decrease in mean CMT was statistically significant ($p = 0.01$) (Tables 1 and 2; Figs. 1, 2, and 3).

Table 1 Changes in central macular thickness and BCVA after subliminal micropulse laser applications in 32 eyes (29 patients)

Patient No	Age	Sex	Eye	CMT		BCVA	
				Before	After	Before	After
1	27	F	R	560	206	91	91
2	46	F	R	647	102	30	54
			L	839	139	0	30
3	28	F	L	650	159	80	80
4	18	F	R	528	126	30	50
5	18	M	R	819	215	50	60
6	47	F	R	637	371	25	35
			L	638	299	4	24
7	67	F	L	589	205	39	45
8	26	F	L	568	189	74	89
9	22	F	R	982	315	74	70
10	29	M	R	522	158	92	92
11	38	M	R	524	204	100	97
12	59	M	L	537	278	70	77
13	57	M	R	582	171	80	87
14	60	F	R	518	385	60	65
15	38	F	R	548	156	91	98
16	45	F	L	595	249	59	74
17	62	M	R	608	309	35	59
18	39	F	R	562	231	74	80
19	22	F	L	659	283	80	80
20	33	M	R	739	362	87	97
			L	668	257	100	98
21	20	M	L	514	175	89	98
22	21	M	R	737	244	74	85
23	30	M	R	571	225	91	95
24	42	F	R	506	204	87	89
25	47	M	L	542	167	74	74
26	21	M	L	500	252	95	95
27	43	F	L	544	379	70	70
28	48	F	L	1270	458	0	0
29	64	M	L	1140	452	35	35

CMT central macular thickness; μm

BCVA best-corrected visual acuity; ETDRS letters

Table 2 Comparison of central macular thickness at baseline and final examination

Central macular thickness	*N* (eye)	Mean $\overline{X}$ (μm)	Standart deviation	*p*
Before SL-MPL	32	651.3	218.2	**0.01***
After SL-MPL	32	247.7	258.1	

SL-MPL, subliminal micropulse laser. *Statistically significant

Median BCVA was 66.8 ETDRS letters before treatment and 70.0 letters at 12 months after treatment. However, the increase in BCVA was not statistically significant ($p = 0.18$) (Tables 1 and 3).

Eighty-six percent of the patients stated that the quality of central vision increased and that color vision, contrast sensitivity, and distortion improved.

We did not encounter any serious adverse events related to the application of SL-MPL. We also did not encounter any scar and atrophic lesions caused by SL-MPL lasers in all subjects.

Discussion

Cystoid macular edema can occur by compensatory, inflammatory, or combined mechanisms in retinitis pigmentosa [7, 8, 15]. Inflammatory edema findings include the presence of white dots in the retinal layers, cells in the vitreous, epiretinal membrane, lipofuscin deposits, flecks, and edema in the form of a petal [8, 16–21]. The signs of compensatory edema are the presence of intraretinal cysts divided by septae and the absence of inflammatory findings [5–9]. There is limited information about the effects of CME on neurodegeneration in RP. The common opinion about CME secondary to RP is that edema should be treated. There are many applications related to CME treatment. Unnecessary treatment or reduction of edema with unsuitable methods can accelerate neurodegeneration [13, 14, 34]. Inflammatory edema accelerates neurodegeneration in RP. Retinal autoantibodies, complement system, and microglial infiltration are common in some types of genetic mutations [16–20]. In these patients, the reduction of edema by appropriate anti-inflammatory treatment can prevent neurodegeneration [25, 26]. Compensatory edema occurs with Müller cell hypertrophy. It is observed that the ellipsoid zone is well protected in edema regions [5–12]. The ellipsoid zone loss is accelerated after treatment with anti-VEGF agents [13–15, 25, 34]. According to our clinical observations, when

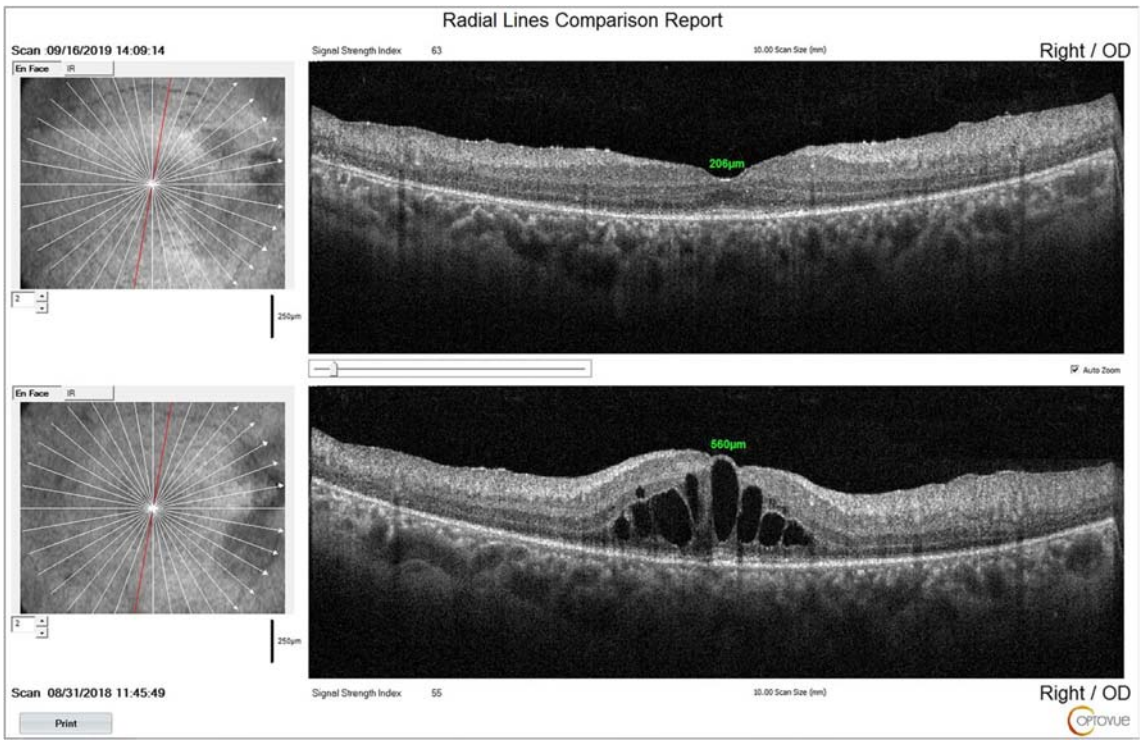

Fig. 1 Central macular thickness changes after SL-MPL application (Table 1; patient no.1, right eye)

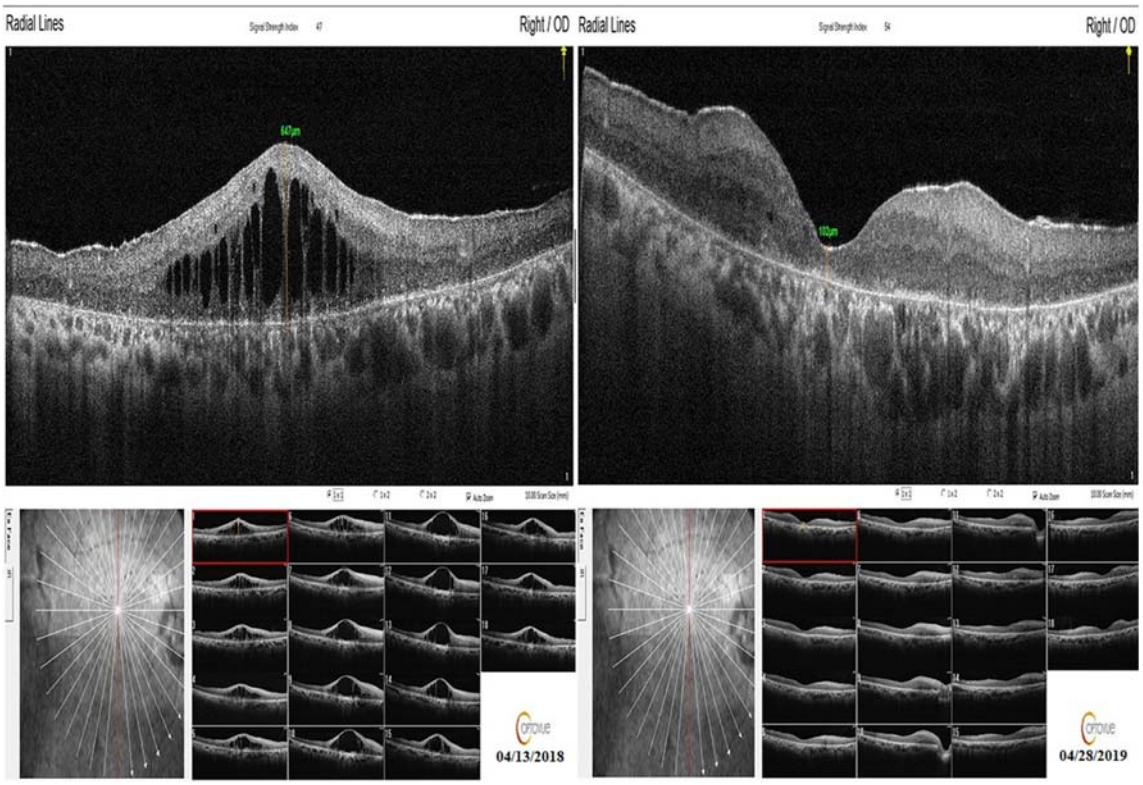

Fig. 2 Central macular thickness changes after SL-MPL application (Table 1; patient no.2, right eye)

the central macular thickness exceeds 500 µm, deterioration in central visual quality develops, such as micropsy, macropsy, blurred vision, loss of contrast, and image distortion. Excessive edema might accelerate neurodegeneration by

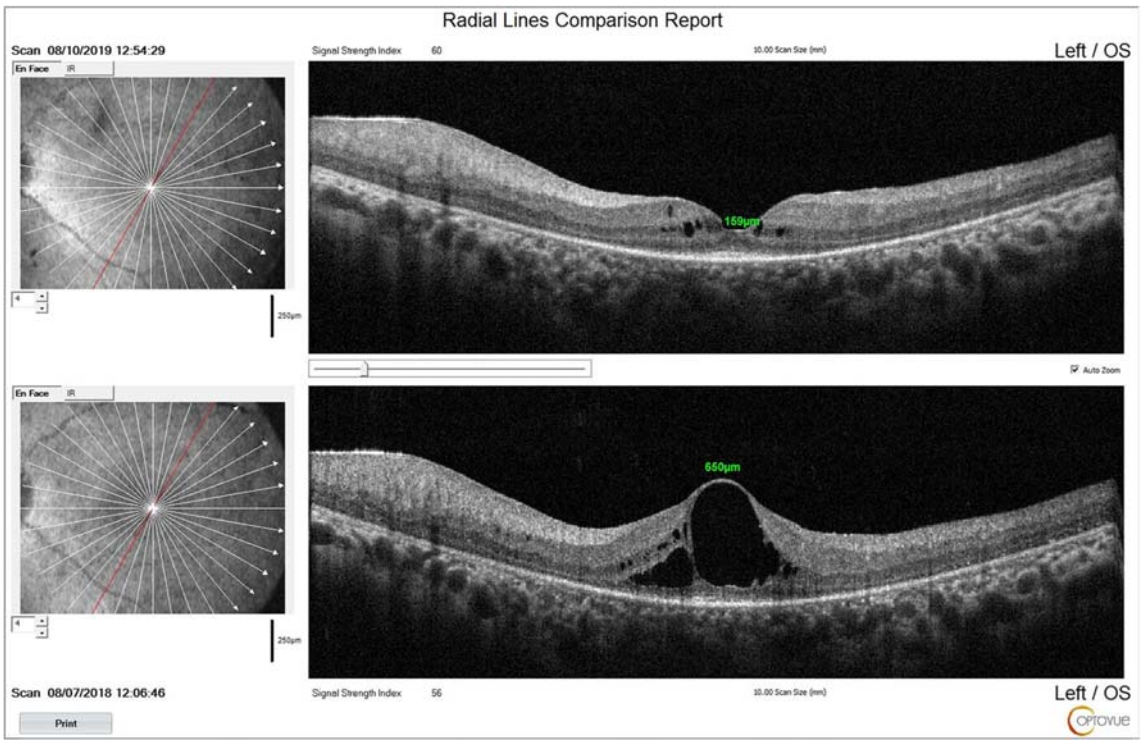

Fig. 3 Central macular thickness changes after SL-MPL application (Table 1; patient no.3, left eye)

Table 3 Comparison of BCVA at baseline and final examination

BCVA	*N* (eye)	Mean $\overline{X}$ (letters)	Standart deviation	*p*
Before SL-MPL	32	66.8	28,10	0.18*
After SL-MPL	32	70.0	26,50	

BCVA, best-corrected visual acuity; *SL-MPL*, subliminal micropulse laser. *Statistically non-significant

disrupting the internal retinal folds and disrupting synaptic connections. Compensatory edema of more than 500 μm should be reduced with an appropriate method.

The mechanism of action of SL-MPL is explained by the reset theory. Reset theory is activating retinal pigment epithelial heat-shock proteins. Subletally induced RPE cells lead to the release of some restorative growth factors (GFs) and suppression of some inflammatory cytokines which restores the pathologic imbalance, ultimately leading to the normalization of GFs, and cytokine expression occurs retinal autoregulation [28–33]. In our study, we observed that SL-MPL significantly reduced the retinal edema and intraretinal cysts. In our opinion, this effect can be explained by an increase in GFs synthesis from activating RPE. The need for alternatively GFs synthesis is reduced from Müller cells. We think that there might be degranulation and shrinkage in microcysts by the stimulation of Müller cells with SL-MPL. Micropulse laser energy is absorbed by the pigments in the retina. Pigmentation levels are variable in RP patients. For this reason, in order to prevent thermal damage, the most appropriate energy dose should be adjusted with a single-spot test in the temporal macula. Pigment densities in the retina also differ according to localizations. The pigment densities of the macular and peripheral retina are different. For this reason, single-spot test should be done in the region close to the macula. Otherwise burns may occur in the macula. The temporal macula is similar to fovea in terms of pigment density. The application energy we detected with single-spot test was generally between 375 and 450 mW. Not to exceed these values may be considered as a further safety measure. All of the patients stated that there was a decrease in visual quality in the first month after SL-MPL application. We think this is due to the change in GF levels in the microenvironment. If the single-spot test is done correctly, there is no possibility of burns. Patients should be informed before the procedure that there may be a temporary decrease in visual quality for 1 month after treatment.

In our study, there was a significant decrease in retinal edema, but there was no significant difference in BCVA after 12 months. Although there is no change in visual acuity of the center, 86% of the patients stated that the quality of central vision increased and that color vision, contrast sensitivity, and distortion improved. This situation might be explained by the fact that the visual acuity and quality of RP are related to the metabolically active photoreceptor cell count. With the application of SL-MPL, although the GF level increases in the microenvironment, there is no effect on the cells undergoing apoptosis. GFs can only reactivate photoreceptors in dormant phase [35–37]. We observed increases in visual acuity in patients whose BCVA values were very low at baseline. We think this is related to the decrease in central vision distortion due to the regression of edema.

This clinical trial has several limitations. Frequency of recurrence of edema; repeatability of SL-MPL; the effect on other visual functions, such as contrast sensitivity; and positive or negative effects on photoreceptor degeneration should be investigated with long follow-ups. How this will affect combined edema, whether other anti-inflammatory treatments and SL-MPL can be combined, is a separate research topic.

Conclusion

The subliminal micropulse yellow laser seems to be a viable therapeutic option in appropriately selected cases. SL-MPL appears to be an effective and safe method in non-inflammatory and resistant CME in RP patients. We detected no serious adverse events and no ophthalmic or systemic side effects during 12 months follow-up.

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Data availability The datasets generated during and/or analyzed during the study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethics committee approval for the subliminal micropulse laser study was obtained from the Ankara University Faculty of Medicine Clinical Research Ethics Committee (20-1249-17). The study was performed in accordance with the tenets of the 2013 Declaration of Helsinki. Written informed consent was obtained from the patients prior to enrollment.

Authorship All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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