Research Article

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Regenerative Medicine

Treatment of resistant chronic central serous chorioretinopathy via platelet-rich plasma with electromagnetic stimulation

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Background: To evaluate whether subtenon injection of platelet-rich plasma (PRP) with retinal electromagnetic stimulation (rEMS) is effective in therapy-resistant chronic central serous chorioretinopathy (CSCR). **Design:** Prospective, sequential. **Materials & methods:** The study included 22 eyes with resistant chronic CSCR. Cases receiving micropulse laser or additional photodynamic therapy, subtenon PRP, and subtenon PRP + rEMS were classified as times 1, 2 and 3, respectively. **Results:** At time 3, the mean best-corrected visual acuity was 85.7 and 97.0 letters before and after the procedures, respectively ($p = 0.01$). Submacular thickness improved by 17, 27 and 51% at times 1, 2 and 3 respectively. **Conclusion:** For treating resistant CSCR, subtenon PRP + rEMS should be considered as an effective and safe option.

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Keywords: central serous chorioretinopathy • electromagnetic stimulation • growth factors • iontophoresis • magnovision • platelet-rich plasma

Central serous chorioretinopathy (CSCR) is a mostly unilateral retinal disorder that predominantly affects middle-aged men. Serous neuroretinal detachment occurs due to fluid accumulation in the submacular area via leakage through the damaged retinal pigment epithelium (RPE) layer [1,2]. The main risk factors for CSCR are emotional stress (type A personality), systemic arterial hypertension, corticosteroid use, sympathomimetic drug use, pregnancy, Cushing's syndrome, the presence of large choroid vessels under the RPE layer and an increase in choroidal thickness (pachychoroid) [3]. CSCR may be classified as acute or chronic. The acute form regresses spontaneously without causing damage; the chronic form progresses and some subretinal fluid can persist. Vision prognosis is worse if serous retinal detachment continues for more than 3–6 months because of the progressive photoreceptor loss [2,4]. In chronic CSCR, widespread RPE changes and diffuse multifocal hyperfluorescent areas are seen in fluorescein angiography (FA) and indocyanine green angiography (ICGA) [1,2]. In etiopathogenesis, RPE cells, choroidea or both are thought to be dysfunctional. Various treatments – including acetazolamide, mineralocorticoid receptor antagonists, intravitreal anti-VEGF injections, subthreshold micropulse laser (MPL) applications and photodynamic therapy (PDT) – are used depending on the stage of the disease [5,6]. However, some cases may be resistant or unresponsive to treatment due to the complex etiopathogenesis. New treatment options and approaches are needed to reduce serious complications. In addition to choroidal congestion, deep retinal capillary ischemia and widespread RPE dysfunction contribute to the pathogenesis of therapy-resistant chronic CSCR [4,7]. Deep retinal capillary ischemia and RPE dysfunction can be treated with restorative-regenerative growth factors [8].

Platelets are enucleated cells that produce several growth factors (GFs), including epithelial, fibroblast, transforming, nerve, platelet-derived and insulin-like. GFs and their receptors, expressed in epithelial and endothelial cells, play a key role in tissue healing. EGF stimulates the proliferation and migration of epithelial cells. NGF is a neurotrophin that stimulates the growth and maintenance of intraretinal glial cells, Müller cells, and neurons [9,10]. Platelet-rich plasma (PRP) contains many GFs and autologous PRP (aPRP) is used in the treatment of retinitis

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pigmentosa and deep retinal capillary ischemia; such treatment has produced promising functional and structural improvements [8,11].

Repetitive high-frequency electromagnetic stimulation/iontophoresis (rEMS/IP) is a physical treatment method that promotes wound healing and epithelialzation by increasing the synthesis and affinity of the tyrosine kinase (Trk) receptor and local blood flow [13]. Moreover, it improves epithelial integrity and neural function by altering the balance of GFs and Trk receptor activity in the damaged microenvironment [13–16]. However, the iontophoresis may increase the passage of active molecules at the tissue level [17–20]. Positive results can be obtained by combining rEMS/IP and aPRP in deep retinal capillary ischemia resulting from various etiologies and without a known treatment [8].

In this prospective clinical study, different treatment methods were compared as sequential phases. The goal was to demonstrate the effectiveness of rEMS/IP and to use subtenon aPRP as a new treatment approach in eyes with chronic CSCR, where current treatment methods are insufficient.

Materials & methods

Approval for the study was obtained from the Ankara University Medical School Clinical Research Ethics Committee (17-1177-18) and Republic of Turkey Ministry of Health Drug and Medical Device Department (2018-136). This research was carried out in accordance with the principles of the Helsinki Declaration. Written consent forms were obtained from the patients before starting the study.

This prospective, open-label, sequentially controlled clinical study in a single group was conducted between December 2018 and September 2019 at Ankara University Faculty of Medicine, Department of Ophthalmology. The study group consisted of 22 unilateral eyes of 22 patients with chronic CSCR who were resistant or unresponsive to current treatment methods.

Diagnostic criteria for chronic CSCR in patients with typical complaints & clinical history

1. The presence of chronic subretinal fluid and elongated outer segments of the photoreceptors on B-scan spectral domain optical coherence tomography (OCT) (Heidelberg-RA2, SW-FAF 488 nm, Germany);
2. Widespread atrophic changes in the RPE layer and/or the presence of serous pigment epithelial detachment (PED);
3. Presence of thick choroid or wide choroid vessels (pachychoroid) on enhanced depth imaging spectral domain OCT;
4. A typical view of the boundaries between chronic subretinal fluid and hyperfluorescent fluorophores in the fundus autofluorescence examination;
5. FA and ICGA examinations were performed simultaneously to detect choroidal neovascularization (CNV) or polypoidal choroidal vasculopathy in suspect eyes with flat irregular PED and chronic subretinal fluid.

Subjects

Inclusion criteria

Eyes with chronic CSCR containing one or more of the following findings constituted the study group (22 unilateral eyes of 22 patients):

1. Symptoms lasting longer than 6 months with relapses.
2. The eyes do not respond or are resistant to all known current treatment methods, including half-fluence PDT and sub-threshold MPL or drugs (acetazolamide, mineralocorticoid receptor antagonists).
3. Presence of widespread RPE changes, atrophic foci and chronic serous retinal detachment areas in the macula and/or outside the macula.

Exclusion criteria

1. Presence of CNV secondary to chronic CSCR;
2. Presence of cataract or dense vitreous opacities (capillary density measurement cannot be done correctly in these cases);
3. Patients taking oral corticosteroids or mineralocorticoid receptor antagonists;
4. The eyes respond well to MPL or PDT.

Time frame

Time 1

MPL was first applied to patients with symptoms lasting for more than 6 months, with chronic signs. Cases with good response to MPL were excluded from the study. We waited at least 3 months for the response to MPL. PDT was performed on MPL-resistant cases. Cases that responded well to PDT were excluded from the study. At least 3 months passed before the response to PDT.

Time 2

Only subtenon aPRP injection was applied to MPL- or PDT-resistant cases. PRP injection was performed three times at 2-week intervals. Patients who responded well after three PRP injections in 1 month were excluded from the study.

Time 3

rEMS/IP combined with subtenon aPRP injection was applied to aPRP-resistant cases. At least 1 month was allowed to elapse after the last aPRP injection. In this group, rEMS/IP was applied daily for 30 min on 10 consecutive days. Subtenon PRP injections were applied on the 1st, 5th and 10th days of the 10-day therapy (a total of three injections). Responses to treatment were evaluated in the first month after the procedures.

We then evaluated new treatment methods applied to the study group at three times according to the 'sequential processes' method [21,22]. The cases were analyzed in three consecutive stages:

Stage 1

This consisted of 22 eyes of 22 patients with chronic symptoms lasting more than 6 months. MPL or, if required, PDT was applied to this group. Necessary consultations for the underlying cause were requested (Table 1).

Stage 2

This was a consecutive group of 22 eyes of 22 patients who did not respond to classical treatments. Subtenon fresh aPRP injections were applied to this group for three sessions at 2-week intervals (Table 2).

Stage 3

This was a consecutive group of 22 eyes of 22 patients who did not respond to aPRP injections. This group received rEMS/IP application for 10 consecutive days and subtenon aPRP injections on the 1st, 5th, and 10th days (Table 3).

The formation of the time 1, 2 and 3 groups after the inclusion and exclusion criteria were applied is seen in the flow diagram (Figure 1).

Two new treatment methods were applied and evaluated over approximately 10 months to a single study group in consecutive stages. Treatment efficacy was compared within and between time groups. Complete ophthalmologic examination was performed on all patients. Best-corrected visual acuity (BCVA) was measured using Early Treatment Diabetic Retinopathy Study cards (Topcon CC 100 XP, Japan). Changes after treatments were evaluated simultaneously via multimodal imaging using the optic coherence tomography angiography (OCTA) device (Optovue Inc., CA, USA). Projection artifacts were removed by activating the 'artifact removal' function of the OCTA device. Thus deep capillary density could be measured accurately.

Quantitative follow-up parameters

1. Submacular thickness (SMT, μm): the space between the ellipsoid zone and Bruch's membrane, manually measured where the volume of the submacular fluid is the highest.
2. Central macular thickness (CMT, μm): the macular thickness between the internal limiting membrane and Bruch's membrane, automatically measured using an OCTA device.
3. Deep retinal capillary density (DRCD, %): automatically calculated using the 'AngioAnalytic' software of the OCTA device and displayed as a sequential density map. The 'Link-B Scans' function of the device was activated to compare vessel densities in exactly the same sections during follow-up.

The primary outcome measure of the study is the difference in BCVA as an indicator of functional changes. Secondary outcome measures are the differences in SMT, CMT and DRCD, which represent structural changes.

Table 1. Time 1: demographic and medical data and treatment response parameters for patients with chronic central serous chorioretinopathy who underwent photodynamic therapy after micropulse laser or micropulse laser.

No	Age (years)/sex	Application	Medical status	Eye (n = 22)	SMT (μm)		CMT (μm)		DRCD (%)		BCVA†	
					Before	After	Before	After	Before	After	Before	After
1	47 M	MPL + PDT	Hypertension Type A	R	312	220	426	334	57.7	40.7	35	35
2	45 M	MPL + PDT	Hypertension Type A	L	380	321	482	419	54.4	33.6	92	80
3	28 M	MPL	Type A personality	L	479	350	570	456	55.0	54.4	94	94
4	59 M	MPL + PDT	Obstructive lung Steroid use	R	270	202	373	305	50.8	45.0	74	70
5	48 M	MPL	Type A personality	L	292	236	384	338	46.6	45.9	80	80
6	44 M	MPL	Hypertension Type A	L	478	376	582	480	50.1	47.9	80	90
7	45 F	MPL	Rheumatoid arthritis Steroid use	L	332	242	421	335	49.6	49.2	74	74
8	51 F	MPL	Brucella arthritis Steroid use	R	257	186	389	311	44.3	43.5	15	20
9	41 M	MPL + PDT	Hypertension Type A personality	R	344	291	466	433	59.8	50.4	91	80
10	46 M	MPL	Type A personality	L	351	322	407	386	55.9	55.9	95	95
11	43 M	MPL	Ulcerative colitis Steroid use	L	404	381	552	537	53.5	52.0	70	80
12	34 M	MPL	Type A personality	L	310	247	421	361	59.8	58.9	92	92
13	35 M	MPL	Bronchial asthma Steroid use	L	151	150	327	325	49.2	47.9	92	92
14	60 F	MPL + PDT	Obstructive lung Steroid use	R	265	232	416	386	45.2	40.7	80	70
15	49 M	MPL + PDT	Hypertension Type A	R	247	132	356	244	50.2	46.2	74	70
16	37 M	MPL	Chronic urticaria Steroid use	R	401	317	497	397	56.9	54.1	80	80
17	52 F	MPL	Fibromyalgia Steroid use	R	408	311	509	432	58.7	55.1	80	80
18	42 M	MPL	Type A personality	R	220	197	396	357	51.5	51.1	80	80
19	36 M	MPL	Hypertension	L	593	490	716	601	46.5	46.3	92	92
20	49 M	MPL	Chronic urticaria Steroid use	R	242	226	341	321	50.1	50.9	98	100
21	39 M	MPL	Hypertension Hypothyroid	L	307	312	409	416	48.8	48.0	94	100
22	46 M	MPL	Hypertension	R	298	291	401	390	54.1	54.2	100	100

† Measured using the Early Treatment Diabetic Retinopathy Study letters.

BCVA: Best-corrected visual acuity; CMT: Central macular thickness; DRCD: Deep retinal capillary density; MPL: Micropulse laser; PDT: Photodynamic therapy; SMT: Submacular thickness.

PRP preparation & application

20 ml of blood was taken from the antecubital vein of the patients and placed into two sterile sodium citrate PRP tubes (T-LAB Kit, T-Biotech, Turkey). The PRP tubes were centrifuged in a refrigerated (4.0°C) centrifuge (1200 NF, Nüve Technology Turkey) at 2500 rpm for 8 min. The lower one-third of the upper plasma was drawn into a 2.5-ml sterile syringe. This plasma is rich in GFs. For each application, 1.5 ml of fresh aPRP suspension was injected into the subtenon space under topical anesthesia. Injections were performed under sterile conditions with a 26G needle tip from the upper temporal region, which was preferred due to its large absorption area and easy access.

Table 2. Time 2: consecutive central serous chorioretinopathy cases that were resistant to classical treatment modalities and given only subtenon autologous platelet-rich plasma injections.

No	Age (years)/sex	Application	Eye (n = 22)	SMT (μm)		CMT (μm)		DRCD (%)		BCVA†	
				Before	After	Before	After	Before	After	Before	After
1	47 M	PRP	R	220	198	334	298	40.7	56.1	35	50
2	45 M	PRP	L	321	202	419	301	33.6	34.7	80	90
3	28 M	PRP	L	350	242	456	347	54.4	58.2	94	100
4	59 M	PRP	R	202	114	305	216	45.0	51.4	70	74
5	48 M	PRP	L	236	141	338	241	45.9	50.1	80	85
6	44 M	PRP	L	376	291	480	391	47.9	51.3	90	100
7	45 F	PRP	L	242	164	335	252	49.2	51.6	74	80
8	51 F	PRP	R	186	134	311	239	43.5	50.2	20	30
9	41 M	PRP	R	291	239	433	381	50.4	60.0	80	85
10	46 M	PRP	L	322	238	386	293	55.9	57.9	95	100
11	43 M	PRP	L	381	299	537	441	52.0	54.1	80	85
12	34 M	PRP	L	247	151	361	272	58.9	60.0	92	100
13	35 M	PRP	L	150	136	325	301	47.9	50.0	92	95
14	60 F	PRP	R	232	135	386	281	40.7	43.3	70	80
15	49 M	PRP	R	132	110	244	221	46.2	49.7	70	74
16	37 M	PRP	R	317	237	397	322	54.1	58.9	80	90
17	52 F	PRP	R	311	182	432	288	55.1	58.5	80	85
18	42 M	PRP	R	197	171	357	322	51.1	52.6	80	90
19	36 M	PRP	L	490	296	601	424	46.3	50.9	92	92
20	49 M	PRP	R	226	198	321	292	50.9	51.4	100	100
21	39 M	PRP	L	312	216	416	317	48.0	51.6	100	100
22	46 M	PRP	R	291	246	390	344	54.2	56.0	100	100

† Measured using the Early Treatment Diabetic Retinopathy Study letters.

BCVA: Best-corrected visual acuity; CMT: Central macular thickness; DRCD: Deep retinal capillary density; PRP: Platelet-rich plasma; SMT: Submacular thickness.

rEMS/IP

rEMS/IP was applied in the form of a helmet with a medical device containing coils designed to stimulate the retina, optic nerve and visual pathways (Magnovision MG10, Bioretina Biyoteknoloji, Turkey). rEMS/IP was applied just before PRP with an electromagnetic field intensity of 2000 mG at 42 Hz for 30 min. These parameters were determined to be effective and safe in clinical and preclinical studies and are recommended by the manufacturer.

Statistical analysis

Mean changes in BCVA, SMT, CMT and DRCD values were calculated as standard deviation. Here, a paired Wilcoxon test analysis was performed to examine the pre- and post-treatment measurements of the group. The Kruskal–Wallis test was performed to examine differences between pre- and post-treatment measurements according to different groups. In order to identify different groups, a double comparison was made using the Mann–Whitney U test. The study was carried out using the SPSS 22.00 package (IBM Corp, NY, USA). The critical decision-making value α was set at 0.05.

Results

The study group consisted of 22 unilateral eyes of 22 patients who did not respond or were resistant to various treatments (16 eyes MPL, 6 eyes MPL + PDT). The aPRP and rEMS/IP methods were applied at time 3 and compared with consecutive stages. Eighteen patients were male and four were female; their mean age was 44.4 years (range: 28–60). Eight patients had systemic diastolic hypertension and nine had a history of cortisone use for chronic diseases. Type A personality was seen in 10 of 22 patients. All cases had chronic CSCR sequelae findings in the fellow eye, such as an RPE irregularity or pachydrusen.

Table 3. Time 3; consecutive central serous chorioretinopathy cases that did not respond after subtenon autologous platelet-rich plasma injection and applied autologous platelet-rich plasma in combination with retinal electromagnetic stimulation/iontophoresis.

No	Age (years)/sex	Application	Eye (n = 22)	SMT (μm)		CMT (μm)		DRCD (%)		BCVA†	
				Before	After	Before	After	Before	After	Before	After
1	47 M	rEMS/IP + PRP	R	198	96	298	218	56.1	56.7	50	70
2	45 M	rEMS/IP + PRP	L	202	124	301	243	34.7	56.7	90	110
3	28 M	rEMS/IP + PRP	L	242	86	347	224	58.2	63.2	100	110
4	59 M	rEMS/IP + PRP	R	114	77	216	146	51.4	57.0	74	89
5	48 M	rEMS/IP + PRP	L	141	88	241	202	50.1	55.0	85	91
6	44 M	rEMS/IP + PRP	L	291	89	391	219	51.3	56.9	100	110
7	45 F	rEMS/IP + PRP	L	164	79	252	180	51.6	55.6	80	83
8	51 F	rEMS/IP + PRP	R	134	94	239	206	50.2	61.5	30	45
9	41 M	rEMS/IP + PRP	R	239	87	381	233	60.0	60.4	85	100
10	46 M	rEMS/IP + PRP	L	238	82	293	226	57.9	59.9	100	110
11	43 M	rEMS/IP + PRP	L	299	96	441	257	54.1	58.0	85	85
12	34 M	rEMS/IP + PRP	L	151	81	272	217	60.0	60.2	100	110
13	35 M	rEMS/IP + PRP	L	136	90	301	225	50.0	57.7	95	97
14	60 F	rEMS/IP + PRP	R	135	86	281	193	43.3	50.7	80	89
15	49 M	rEMS/IP + PRP	R	110	82	221	186	49.7	54.2	74	83
16	37 M	rEMS/IP + PRP	R	237	102	322	238	58.9	61.0	90	110
17	52 F	rEMS/IP + PRP	R	182	97	288	222	58.5	62.5	85	91
18	42 M	rEMS/IP + PRP	R	171	88	322	227	52.6	57.1	90	110
19	36 M	rEMS/IP + PRP	L	296	71	424	224	50.9	54.9	92	110
20	49 M	rEMS/IP + PRP	R	198	90	292	201	51.4	54.9	100	110
21	39 M	rEMS/IP + PRP	L	216	84	317	216	51.6	57.0	100	110
22	46 M	rEMS/IP + PRP	R	246	87	344	201	56.0	58.2	100	110

†Measured using the Early Treatment Diabetic Retinopathy Study letters.
BCVA: Best-corrected visual acuity; CMT: Central macular thickness; DRCD: Deep retinal capillary density; PRP: Platelet-rich plasma; rEMS/IP: Retinal repetitive electromagnetic stimulation/iontophoresis; SMT: Submacular thickness.

BCVA

At time 1, mean BCVA was 80.1 and 79.7 letters before and after the classical treatment procedures were applied, respectively (p = 0.81). At time 2, mean BCVA was 79.7 and 85.7 letters before and after the aPRP application, respectively (p = 0.72). At time 3, mean BCVA was 85.7 and 97.0 letters before and after the application of aPRP combined with rEMS/IP, respectively (p = 0.01; Δp 3 >1,2) (Tables 1–5). In fellow eyes, mean BCVA was 97 and 97 letters at times 1 and 3, respectively.

SMT

At time 1, mean SMT was 333.7 and 274.2 μm before and after the classical treatment procedures, respectively (p = 0.01). At time 2, mean SMT was 274.2 and 198.1 μm before and after the aPRP applications, respectively (p = 0.01). At time 3, mean SMT was 198.1 and 88.9 μm before and after applying aPRP combined with rEMS/IP, respectively (p = 0.01). A comparison of SMT percentage change showed a 17% improvement at time 1, 27% at time 2, and 51% at time 3 (Δp 3 >2,1). In 19/22 eyes (86.4%), the submacular fluid disappeared completely at time 3 (Figures 2–6, Tables 1–5). In fellow eyes, mean SMT was 90.1 and 90.2 μm at times 1 and 3, respectively.

CMT

At time 1, mean CMTs were 447.3 and 389.7 μm before and after the classical treatment procedures, respectively (p = 0.01). At time 2, mean CMTs were 389.7 and 310.6 μm before and after the aPRP application, respectively (p = 0.01). At time 3, mean CMTs were 310.6 and 213.8 μm before and after applying aPRP combined with rEMS/IP, respectively (p = 0.01). When the CMT percentage changes were compared, a 13% improvement at time

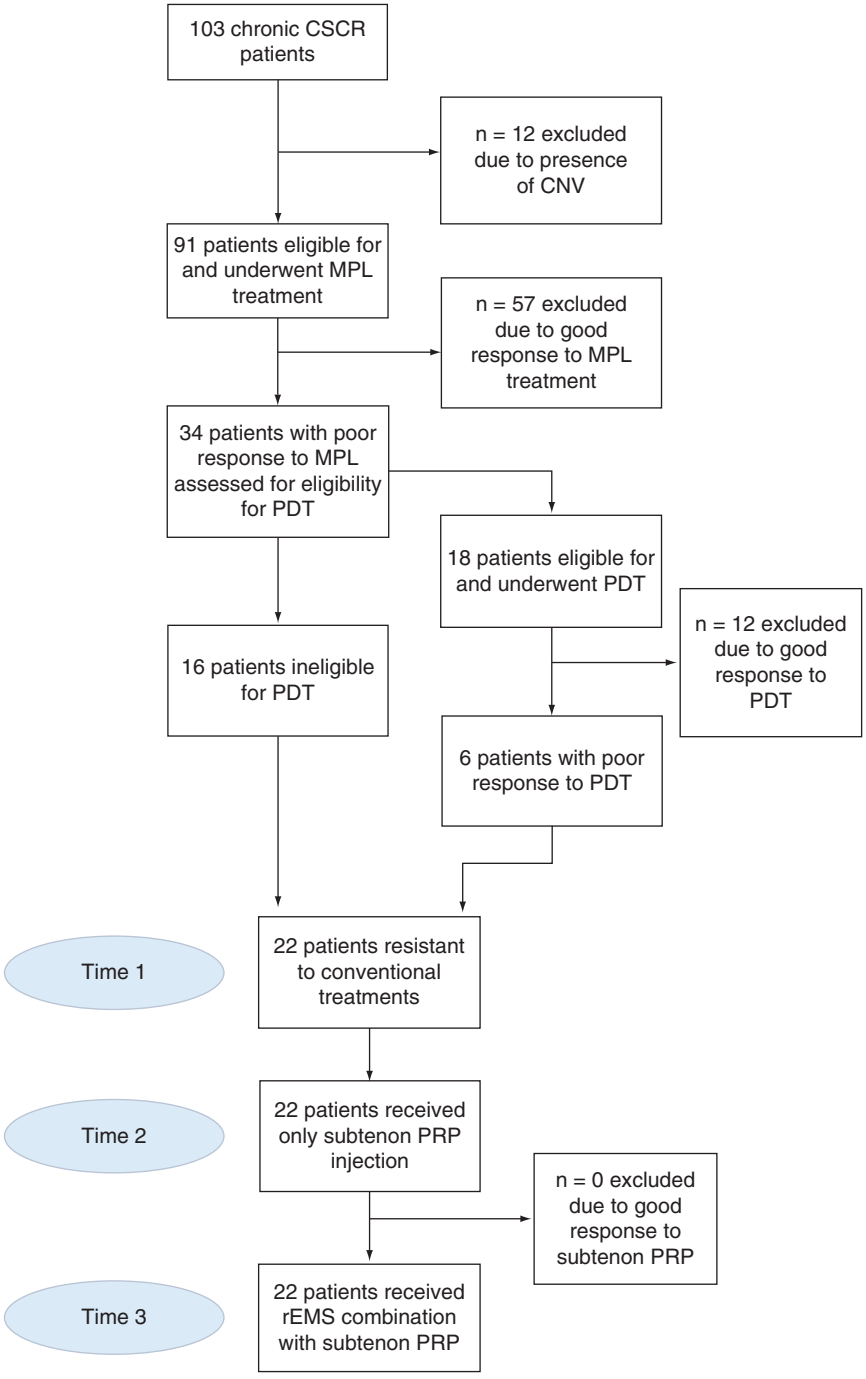

Figure 1. Flow diagram illustrating the formation of the time groups after inclusion and exclusion criteria were applied.
CSCR: Central serous chorioretinopathy; CNV: Choroidal neovascularization; MPL: Micropulse laser; PDT: Photodynamic therapy; PRP: Platelet-rich plasma; rEMS: Retinal repetitive electromagnetic stimulation.

1, 20% at time 2 and 30% at time 3 ($\Delta p\ 3 > 2,1$) was observed (Figures 2–6, Tables 1–5). In fellow eyes, mean CMTs were 221.0 and 223.2 μm at times 1 and 3, respectively.

DRCD

At time 1, mean DRCDs were 52.2 and 48.7% before and after the classical treatment procedures, respectively ($p = 0.03$). At time 2, mean DRCDs were 48.7 and 52.7% before and after the aPRP applications, respectively ($p =$

Table 4. Comparison of follow-up parameters within and between groups.

Times	Time 1 Classical treatments		Time 2 Only aPRP		Time 3 aPRP + rEMS/IP		p-value
Follow-up parameters	Before	After	Before	After	Before	After	
SMT (μm)	333.7	274.2	274.2	198.1	198.1	88.9	**3** >2,1
	p = 0.01		p = 0.01		p = 0.01		
CMT (μm)	447.3	389,7	389.7	310.6	310.6	213.8	**3** >2,1
	p = 0.01		p = 0.01		p = 0.01		
DRCD (%)	52.2	48.7	48.7	52.7	52.7	57.7	**3,2** >1
	p = 0.03		p = 0.01		p = 0.01		
BCVA†	80.1	79.7	79.7	85.7	85.7	97.0	**3** >1,2
	p = 0.81		p = 0.72		p = 0.01		

Kruskal–Wallis test was used for triple comparison; Mann–Whitney *U* test was used for binary comparison. p-value comparison: All parameters were significantly higher in time 3.
† Measured using the Early Treatment Diabetic Retinopathy Study letters.
aPRP: Autologous platelet-rich plasma; BCVA: Best-corrected visual acuity; CMT: Central macular thickness; DRCD: Deep retinal capillary density; rEMS/IP: Retinal repetitive electromagnetic stimulation/iontophoresis; SMT: Submacular thickness.

Table 5. Comparison of percentage and delta changes between groups.

SMT difference (%)			p-value	Comparison
Time 1 (n = 22)	Time 2 (n = 22)	Time 3 (n = 22)		
X ± s.d	X ± s.d	X ± s.d	0.01	**3** >2,1
17±11	27±11	**51±15**		
CMT difference (%)				
X ± s.d	X ± s.d	X ± s.d	0.01	**3** >2,1
13±8	20±8	**30±9**		
DRCD difference (%)				
X ± s.d	X ± s.d	X ± s.d	0.01	3,2 >1
−3.5 ± 2.6	**+4.0 ± 2.4**	**+5.1 ± 2.4**		
BCVA difference†				
X ± s.d	X ± s.s.	X ± s.s.	0.01	**3** >1,2
0.4 ± 1.1	6 ± 1.3	**11.3 ± 1.2**		

Kruskal–Wallis test was used for triple comparison; Mann–Whitney U test was used for binary comparison.
$p < 0.05$ statistically significant, expressed in bold and italics.
†Measured using the Early Treatment Diabetic Retinopathy Study letters.
BCVA: Best-corrected visual acuity; CMT: Central macular thickness; DRCD: Deep retinal capillary density; s.d: Standart deviation; SMT: Submacular thickness (%)

0.01). At time 3, mean DRCDs were 52.7 and 57.7% before and after applying aPRP combined with rEMS/IP, respectively (p = 0.01). The DRCD percentage changed by –3.5% at time 1, +4% at time 2 and +5% at time 3 (Δp 3,2 >1) (Figures 2–5, Tables 1–5). In fellow eyes, mean DRCDs were 55.2 and 56.4% at times 1 and 3, respectively.

No serious ocular or systemic adverse events were encountered during the follow-up in any group related to rEMS/IP or aPRP applications.

Discussion

Acute and chronic CSCR differ in clinical presentation and prognosis. In acute CSCR a sudden deterioration in central vision occurs as a result of rapid accumulation of fluid in the submacular area. Impairments in color vision and dark adaptation, central or paracentral scotoma and metamorphopsia or micropsia are also observed [2,5]. The acute form usually heals spontaneously and without sequelae, but if the chronic form is not treated, progressive vision loss develops. The outer segments of the photoreceptor may appear elongated on B-scan spectral domain OCT. Flat irregular PEDs may be surrounded by subretinal fluid containing fibrin/fluorophore [4,7,12]. Diffuse RPE irregularities, intraretinal fluid accumulation, cystic retinal changes, retinal atrophy, subretinal fibrinous accumulation, fibrosis and secondary CNV are late complications and can cause permanent visual loss [1–3,6–8]. The pathophysiology of CSCR is not fully understood. RPE dysfunction and loss of integrity may be due to the

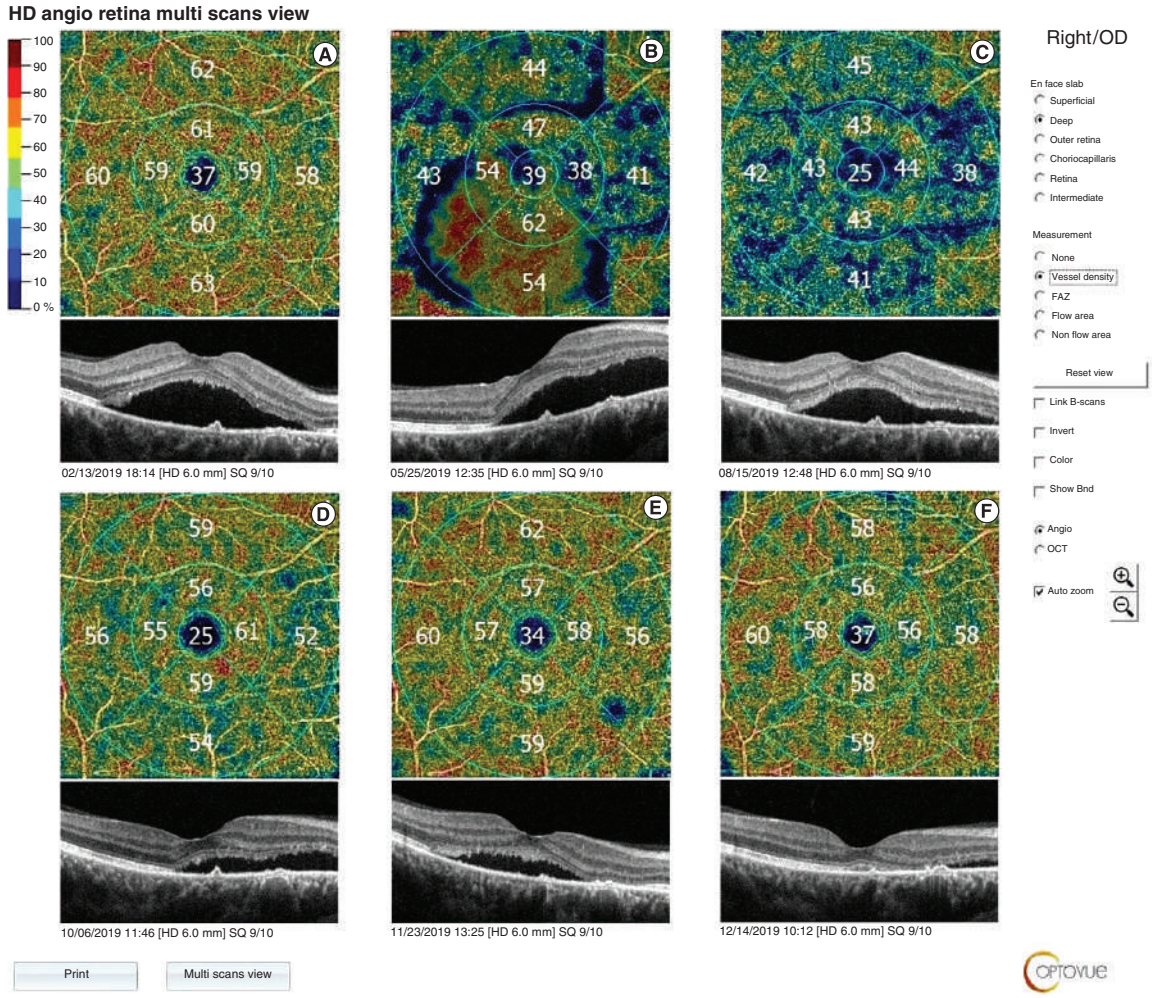

Figure 2. Submacular thickness and deep retinal capillary density changes according to time groups (patient 1). (A–C) First MPL then PDT were applied at time 1 (SMT: 312 μm before, 220 μm after application; DRCD: 57.7% before and 40.7% after application). **(D)** Only aPRP was applied at time 2 (SMT: 220 μm before, 198 μm after application; DRCD: 40.7% before and 56.1% after application). **(E)** rEMS/IP combined with aPRP were applied at time 3 (SMT: 198 μm before application; DRCD: 56.1% before application). **(F)** After combined application (SMT: 96 μm after application; DRCD: 56.7% after application), see also Tables 1–3.
aPRP: Autologous platelet-rich plasma; DRCD: Deep retinal capillary density; MPL: Micropulse laser; OD: Right eye; PDT: Photodynamic therapy; rEMS/IP: Retinal repetitive electromagnetic stimulation; SMT: Submacular thickness.

increased blood cortisol level and increased choroidal hydrostatic pressure caused by a thick choroid (pachychoroid) or high systemic arterial diastolic pressure. Thick choroidea and wide vessels can be visualized by swept-source OCT and by enhanced depth imaging spectral domain OCT [4,7,12]. These findings support the hypothesis that the choroidea vasculature is congested and extremely permeable in CSCR, as seen with ICGA [1–3,6–8]. OCTA has become the gold standard in the diagnosis and follow-up of retinal disease. FA and ICG are invasive procedures, whereas OCTA provides detailed anatomical and vascular structure information of the retinal and choroidal layers with a single noninvasive scan. FA and ICGA are used in the differential diagnosis of latent CNV or polypoidal vasculopathy when suspicious irregular PED is detected in OCTA.

High blood cortisol levels disrupt Trk receptor activity and balance between various GFs. The integrity of the zonula occludens between RPE cells is then disrupted, and ion channels and fluid movements are affected by the RPE layer. As a result, RPE/photoreceptor damage and dysfunction are observed and visual functions are affected by accumulating fluid under the sensory retina [1–3,6–8]. Because of complex etiopathogenesis, treatments that target only choroidal thickness and leakage – including acetazolamide, intravitreal anti-VEGF injection or PDT – may not be sufficient to correct the underlying pathology [5,6]. In addition to choroidal pathology, widespread RPE

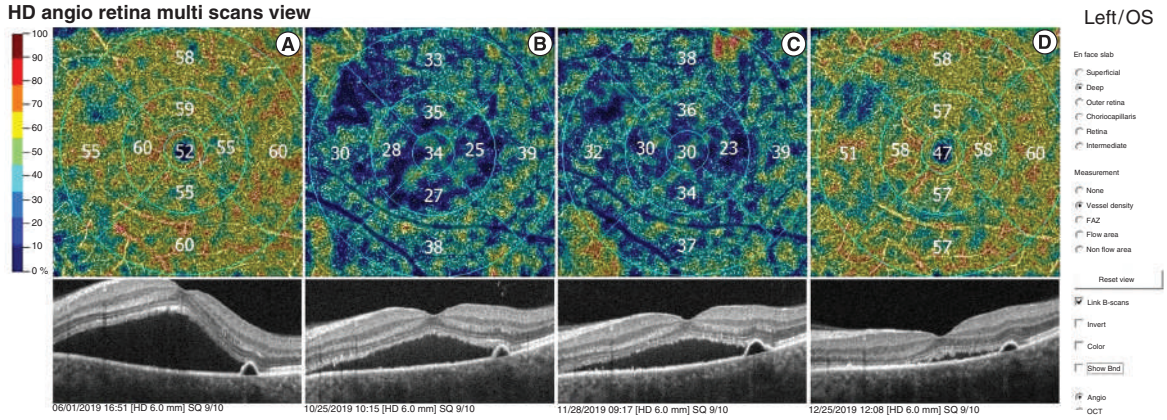

Figure 3. Submacular thickness and deep retinal capillary density changes according to time groups (patient 2). (A) First MPL then PDT were applied at time 1 (SMT: 380 μm before, 321 μm after application; DRCD: 54.4% before, 33.6% after application). **(B)** Only aPRP was applied at time 2 (SMT: 321 μm before, 202 μm after application, DRCD: 33.6% before, 34.7% after application). **(C)** rEMS/IP combined with aPRP were applied at time 3 (SMT: 202 μm before application; DRCD: 34.7% before application). **(D)** After combined application (SMT: 124 μm after application; DRCD: 56.7% after application), see also Tables 1–3.
aPRP: Autologous platelet-rich plasma; DRCD: Deep retinal capillary density; MPL: Micropulse laser; OS: Left eye; PDT: Photodynamic therapy; rEMS/IP: Retinal repetitive electromagnetic stimulation/iontophoresis; SMT: Submacular thickness.

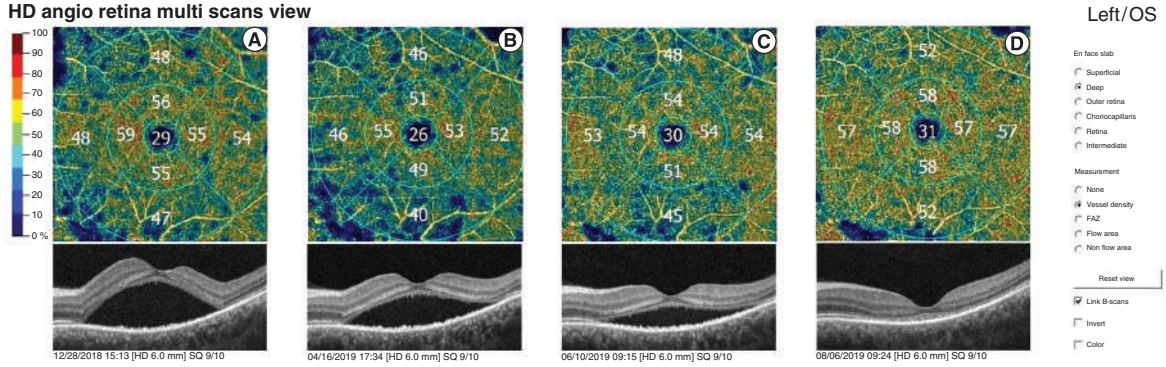

Figure 4. Submacular thickness and deep retinal capillary density changes according to time groups (patient 6). (A) MPL was applied at time 1 (SMT: 478 μm before, 376 μm after application; DRCD: 50.1% before, 47.9% after application). **(B)** Only aPRP was applied at time 2 (SMT: 376 μm before, 291 μm after application; DRCD: 47.9% before, 51.3% after application). **(C)** rEMS/IP combined with aPRP were applied at time 3 (SMT: 291 μm before application; DRCD: 51.3% before application). **(D)** After combined application (SMT: 89 μm after application; DRCD: 56.9% after application), see also Tables 1–3.
aPRP: Autologous platelet-rich plasma; DRCD: Deep retinal capillary density; MPL: Micropulse laser; OS: Left eye; PDT: Photodynamic therapy; rEMS/IP: Retinal repetitive electromagnetic stimulation/iontophoresis; SMT: Submacular thickness.

dysfunction (often accompanied by deep retinal capillary ischemia) can contribute to the development of CSCR. Thus it may be reasonable to support the microenvironment of the outer retinal complex (choriocapillaris–Bruch's membrane–RPE) via restorative GFs. Various treatment methods are currently applied depending on the stage of the disease, the extent of the lesion and the presence of CNV [5,6]. However, some cases may be resistant or unresponsive to current treatments. PDT is generally effective but can only be applied in local RPE defects; it cannot be applied in cases with multifocal diffuse retinal pigment epitheliopathy due to possible complications, including choroidal ischemia, retinal artery occlusion, retinal pigment epithelial atrophy and central scotoma [4–6]. The disease may recur in 15–50% of cases. Bilateral involvement may occur in approximately one-third of cases. Secondary CNV development can be seen in 2–9% of patients with chronic CSCR and seriously threatens vision [1–3,6–8]. In etiopathogenesis, RPE cells, choroidea, or both are thought to dysfunction together. Due to

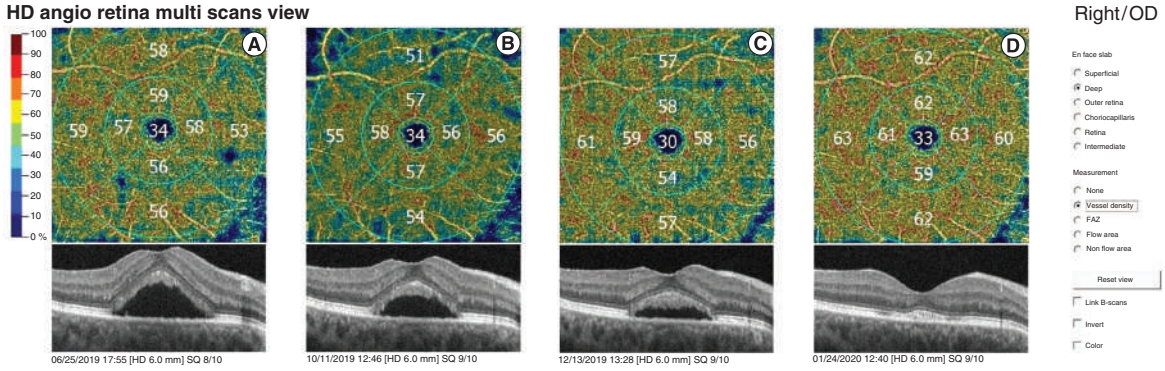

Figure 5. Submacular thickness and deep retinal capillary density changes according to time groups (patient 16). (A) MPL was applied at time 1 (SMT: 401 μm before, 317 μm after application; DRCD: 56.9% before, 54.1% after application). **(B)** Only aPRP was applied at time 2 (SMT: 317 μm before, 237 μm after application; DRCD: 54.1% before, 58.9% after application). **(C)** rEMS/IP combined with aPRP were applied at time 3 (SMT: 237 μm before application; DRCD: 58.9% before application). **(D)** After combined application (SMT: 102 μm after application; DRCD: 61% after application), see also Tables 1–3.
aPRP: Autologous platelet-rich plasma; DRCD: Deep retinal capillary density; MPL: Micropulse laser; OD: Right eye; PDT: Photodynamic therapy; rEMS/IP: Retinal repetitive electromagnetic stimulation/iontophoresis; SMT: Submacular thickness (μm)

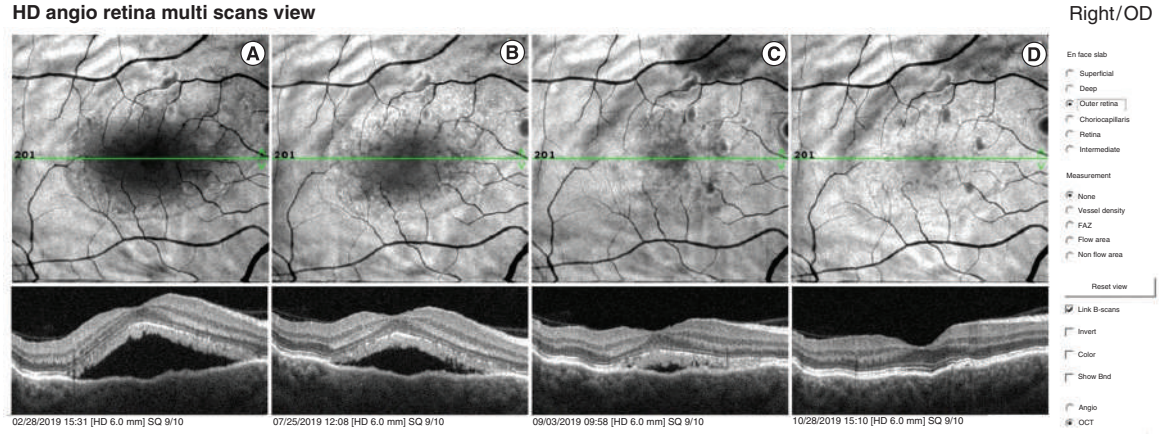

Figure 6. Submacular thickness and central macular thickness changes according to time groups (patient 17). (A) MPL was applied at time 1 (SMT: 408 μm before, 311 μm after application; CMT: 509 μm before, 432 μm after application). **(B)** Only aPRP was applied at time 2 (SMT: 311 μm before, 182 μm after application; CMT: 432 μm before, 288 μm after application). **(C)** rEMS/IP combined with aPRP were applied at time 3 (SMT: 182 μm before application; CMT: 288 μm before application). **(D)** After combined application (SMT 97 μm after application; CMT 222 μm after application), see also Tables 1–3.
aPRP: Autologous platelet-rich plasma; CMT: Central macular thickness; MPL: Micropulse laser; OD: Right eye; rEMS/IP: Retinal repetitive electromagnetic stimulation/iontophoresis; SMT: Submacular thickness.

the complex etiopathogenesis, new treatment options and approaches are needed to reduce serious complications. Thus we investigated the effectiveness of GFs as an alternative and new treatment modality for the treatment of chronic CSCR that cannot be managed by current treatment modalities.

Fresh autologous PRP was used at time 2 as a source of GFs. Submacular fluid decreased significantly and deep retinal capillary blood flow increased significantly at time 2. However, no significant increase in visual acuity was observed. EGF and PDGF play a key role in wound healing and epithelialization. EGF is responsible for epithelial proliferation and integration and PDGF for increasing capillary blood flow [9,16]. NGF is a neurotrophin that stimulates the growth and maintenance of intraretinal glial cells, Müller cells and neurons; it also plays a key role in ensuring the integrity and function of epithelial cells and nerve fibers [9,10].

Scleral pores allow passive diffusion for molecules smaller than 75 kDa. The electrical charges of larger molecules must be changed for them to pass through. For this purpose, electrical or electromagnetic iontophoresis is needed [17–19]. NGF and IGF, both larger than 75 kDa, are responsible for the oxidative phosphorylation required for neural functions [9–11]. We think that when subtenon aPRP is used alone, a significant number of GFs cannot pass from the scleral pores to the choroidal matrix. In our previous study, we showed that the use of rEMS with aPRP is more effective than aPRP alone in the treatment of eyes affected by deep retinal capillary ischemia [8]. Another study proved that aPRP and rEMS are effective in slowing disease progression in patients with retinitis pigmentosa [23].

The prolonged presence of submacular fluid can reduce the ability of RPE to benefit from choroidal circulation. We think that the development of deep retinal capillary ischemia may be the cause of resistance to treatment. GFs in PRP can reduce this ischemia. When we applied subtenon aPRP in combination with rEMS/IP at time 3, the submacular fluid decreased significantly and deep retinal capillary blood flow increased. BCVA significantly increased only at time 3. The GFs in the choroidal matrix can pass to the subretinal space through the Trk receptors [20]. Moreover, rEMS/IP can increase the transition of GFs from scleral pores to the choroidal matrix. Growth factor affinity of Trk receptors can be increased by rEMS [13–20]. At time 3, we can explain the significant increase in visual acuity and all parameters by the iontophoresis effect of rEMS. Coils in the Magnovision helmet form an electromagnetic field without touching the scalp or face. Importantly, the intensity of the electromagnetic field at the tissue level is far below the safety limit defined by WHO [24,25]. PRP, as a growth factor source, can be obtained from the patient at a low cost. The electromagnetic iontophoresis device also seems to be affordable in terms of purchase, periodic maintenance and repair costs. With this method, we found the highest increase in DRCD. The reduction of deep capillary ischemia may have strengthened connections between RPE cells and decreased submacular fluid by increasing the pump function of RPE.

This study has some limitations. The aPRP injections combined with rEMS/IP appear to repair the RPE defect, strengthen the external blood retinal barrier and correct dysfunction due to retinal ischemia. However, long-term follow-up is needed. Determining the relationship between underlying systemic conditions and relapses is a separate research topic. Existing OCTA instruments have some artifact problems. It is important to identify and remove these artifacts to evaluate DRCD accurately in consecutive measurements. Some chronic CSCR cases may recover spontaneously. Causes of disease are not homogeneous. For this reason, it is not possible to create a control group. Another limitation is that we examined the changes according to time periods instead of using an independent control group.

Conclusion

Resistant chronic CSCR is an important socioeconomic and psychological problem in the productive aged population. In the treatment of resistant CSCR, subtenon PRP combined with rEMS should be considered as an effective and safe treatment option. This combined approach can regulate dysfunctional or damaged external retinal microenvironment using the restorative and circulation-enhancing effect of various GFs.

Executive summary

- Central serous chorioretinopathy is a retinal disease that predominantly affects middle-aged men.
- Various treatment methods (e.g., acetazolamide, mineralocorticoid receptor antagonists, intravitreal anti-VEGF injections, sub-threshold micropulse laser applications and photodynamic therapy) are used.
- Some cases may be resistant or unresponsive to current treatments.
- Due to the complex etiopathogenesis, new treatment options and approaches are needed to reduce serious complications.
- We investigated whether subtenon platelet-rich plasma injection combined with retinal electromagnetic stimulation is effective in chronic central serous chorioretinopathy cases resistant to classical therapies.
- A combination of autologous platelet-rich plasma and noninvasive electromagnetic stimulation/iontophoresis is a safe, effective and novel therapeutic approach.
- This combined approach can regulate a dysfunctional or damaged external retinal microenvironment using the restorative and circulatory enhancing effect of various growth factors.

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Financial & competing interests disclosure

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Ethical conduct of research

Approval for the study was obtained from the Ankara University Medical School Clinical Research Ethics Committee (17-1177-18) and Republic of Turkey Ministry of Health Drug and Medical Device Department (2018-136). This research was carried out in accordance with the principles of the Helsinki Declaration. Written consent forms were obtained from the patients before starting the study.

Data sharing statement

The authors certify that this manuscript reports original clinical trial data (ClinicalTrials.gov identifier: NCT04224831). Individual, personal patient data will not be made available however clinical data, the study protocol and statistical analyses will be made available 1 year after publication. Requests should be made to the corresponding author.

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