• Clinical Research •

Umbilical cord derived mesenchymal stem cell implantation in retinitis pigmentosa: a 6-month follow-up results of a phase 3 trial

Neslihan Sinim Kahraman, Ayse Oner

Department of Ophthalmology, Kayseri Acibadem Hospital, Kayseri 38030, Turkey

Correspondence to: Ayse Oner. Department of Ophthalmology, Acibadem Kayseri Hospital, TR-38030, Kayseri, Turkey. aoner@erciyes.edu.tr; ayseozoner@gmail.com

Received: 2020-02-20 Accepted: 2020-03-15

Abstract

● **AIM:** To investigate the efficacy and the safety of umbilical cord derived mesenchymal stem cell (UC-MSC) implantation in patients with retinitis pigmentosa (RP).

● **METHODS:** This prospective, single-center, phase 3 clinical study enrolled 124 eyes of 82 RP patients. The patients received 5 million UC-MSCs to the suprachoroidal area with a surgical procedure. Patients were evaluated on the 1st day, 1st, and 6th months postoperatively. Best corrected visual acuity (BCVA), anterior segment and fundus examinations, color photography, optical coherence tomography (OCT), and visual field (VF) tests were carried out at each visit. Fundus fluorescein angiography (FFA) and multifocal electroretinography (mfERG) recordings were performed at the end of the 6th month. Ocular and systemic adverse events of the surgical procedure were also noted.

● **RESULTS:** All of the 82 patients completed the 6-month follow-up period. None of them had any serious systemic or ocular complications. There were statistically significant improvements in BCVA and VF during the study (all $P<0.05$). The amplitudes of the P1 waves in the central areas showed significant improvements in mfERG recordings. There were also significant increases in implicit times of P1 waves in the central areas.

● **CONCLUSION:** Suprachoroidal administration of UC-MSCs has beneficial effect on BCVA, VF, and mfERG measurements during the 6-month follow-up period. Cell mediated therapy based on the secretion of growth factors (GFs) seems to be an effective and safe option for degenerative retinal diseases.

● **KEYWORDS:** cell mediated therapy; retinitis pigmentosa; suprachoroidal; umbilical cord derived mesenchymal stem cells; visual function

DOI:10.18240/ijo.2020.09.14

Citation: Kahraman NS, Oner A. Umbilical cord derived mesenchymal stem cell implantation in retinitis pigmentosa: a 6-month follow-up results of a phase 3 trial. *Int J Ophthalmol* 2020;13(9):1423-1429

INTRODUCTION

Retinitis pigmentosa (RP) is the most common hereditary retinal disorder which causes degeneration of rod and cone photoreceptors. It has been reported that the inheritance pattern can be autosomal recessive (50%-60%), autosomal dominant (30%-40%) or X-linked (5%-15%) feature. The disease initially begins with night blindness, proceed to loss of central vision and total blindness. To date, there is no definitive cure for patients with RP[1-6].

Rods and cones vitally and functionally depend on the retinal pigment epithelium[7-8]. Various growth factors (GFs) and their receptors are produced in this epithelium and lots of genes are responsible for the production of these GFs. Genetic mutation in any of these genes causes retinal degeneration by ongoing loss of retinal pigment epithelium and photoreceptors[3,9].

Cell replacement therapies have been studied recently as a feasible alternative for different diseases[2,6-7,9]. Mesenchymal stem cells (MSCs) are immature cells which have the ability to self-renewal and differentiate into mature cells. MSCs also provide trophic support for neuroprotection and regeneration of damaged retinal cells either directly through the secretion of neurotrophic factors or indirectly with the paracrine support[2,6,9].

Recent studies reported that umbilical cord-derived MSCs (UC-MSCs) have significant paracrine and immunomodulatory features by producing trophic factors that are similar to those synthesized by retinal pigment epithelium[10-12]. Recent clinical studies reported that UC-MSCs are effective in preventing retinal degeneration and rescuing photoreceptors[11-12]. Experimental studies of degenerative and ischemic retinal disorders demonstrated that UC-MSCs could mitigate chronic inflammation and prevent apoptosis[10].

The discovery of the trophic factors and their importance in promoting photoreceptor survival lead the efforts of developing

cell preservation therapies[13]. Based on the data obtained from previous clinical studies, we conducted a phase 3 clinical trial in patients with RP to evaluate the safety and efficacy of UC-MSC transplantation using a suprachoroidal implantation approach.

SUBJECTS AND METHODS

Ethical Approval The study was performed in accordance with the Declaration of Helsinki, after obtaining the approval of the Ethics Committee of the University (2017/480, 10.13.2017) and the approval by the Review Board of Stem Cell Applications of the Ministry of Health (Registration number: 56733164/203) according to the regulations in our country. Written informed consent was signed by all participants of the study.

Study Design and Setting This prospective open label phase 3 clinical study was performed to evaluate the efficacy and the safety of suprachoroidal UC-MSCs implantation in patients with RP in the Ophthalmology Department of our hospital between 03.01.2019 and 12.30.2019.

Subjects After receiving a complete medical history, the patients were assessed according to the criteria of the study. The inclusion criteria were: 1) age older than 18y; 2) clinical diagnosis of RP confirmed by ophthalmological tests; 3) best corrected visual acuity (BCVA) of <20/50; 4) various degrees of visual field (VF) loss. The exclusion criteria were: 1) ocular surgery except cataract extraction; 2) presence of vitreous opacities that would affect ocular imaging or tests; 3) another ocular disease except RP (*i.e.*, uveitis, strabismus, glaucoma); 4) systemic or neurological disease; 5) the habit of smoking.

Variables and Outcomes After recording the demographic variables, all subjects received a detailed ophthalmic examination including BCVA and intraocular pressure measurements, anterior segment evaluation, color fundus photography, optical coherence tomography (OCT), fundus fluorescein angiography (FFA), VF, and multifocal electroretinography (mfERG) tests.

The BCVA, VF, and mfERG outputs were three primary outcomes of our study. VF examination was performed by Humphrey VF analyzer device (Carl Zeiss Meditec AG Germany), program 30-2 was used for testing of each eye. BCVA was evaluated with a Snellen chart at a distance of 3 m and presented as the logarithm of the minimum angle of resolution (logMAR). mfERG was recorded on mfERG Vision monitor (Metrovision, France). The mfERG test was performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines[14].

During the mfERG evaluations, a matrix of 61 hexagons of the individual mfERG responses were generated, and these hexagons were grouped into five concentric rings (<2°, 2°-5°, 5°-10°, 1°-15°, and >15°) centered on the fovea. We recorded the average amplitude and implicit time of the first positive wave (P1) in these five rings.

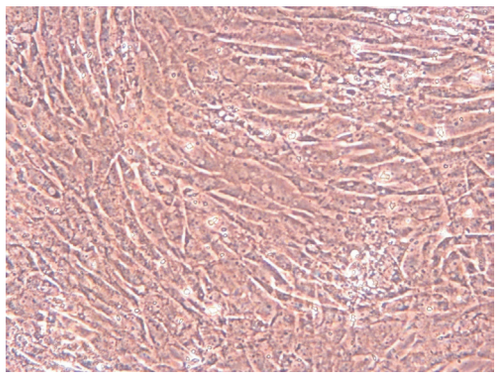

Figure 1 Morphological appearance of UC-MSCs.

Another primary outcome was to report the adverse events related to the stem cell implantation and surgical procedure. We defined the adverse events as the presence of ocular (intraocular/intraorbital inflammation, infection, tumor formation, proptosis, diplopia or strabismus, corneal pathology, allergic reaction, any retinal pathology, vitreoretinal problem, intraocular pressure alteration, optic nerve pathology) or systemic complications.

Stem Cell Preparation Umbilical cord was disinfected, cut into pieces of 1-2 mm^2 and transferred to 75 cm^2 culture flasks in Dulbecco's modified Eagle's medium-low glucose (DMEM-LG) containing a concentration of 10% human serum and of 1% penicillin/streptomycin. The cells were cultured at 37°C with 5% density of CO_2. Every 3d, the culture medium was removed and fresh medium was added until the cells reached minimum 70% confluency (Figure 1). After the third passage the cells were analyzed with flow cytometry for confirmation of phenotypic characteristics. The UC-MSCs were positive for CD-73, CD-90, and CD-105, and negative for CD-34, CD-45, and HLA-DR. The procedure of stem cell preparation was performed under good manufacturing practice (GMP) conditions and before release UC-MSCs were assessed for cell appearance, viability, identification, purity, content, and potency. The cells were also screened for bacterial or fungal contamination. Cell viability was >90.0%±0.5% before cell transplantation. A concentration of 5×10^6 cells in isotonic solution containing 1% human serum albumin were carried in 2 mL vials which was placed in a sterile tube. The tubes were transfered with the temperature-controlled bag (set at a temperature between 2°C-8°C) until the cells reach the operating room. The cells were used in 24h.

Surgical Procedures An experienced surgeon (Oner A) performed all surgeries. All operations were done with local anesthesia. The surgical technique was known as Limoli retinal restoration technique (LRRT), which was described by Limoli *et al*[15-17]. It was also used by our group in our previous studies[18-19]. The stem cell suspension was injected to the transplanted fat tissue between the choroid and sclera. However, we used a different stem cell source with a different

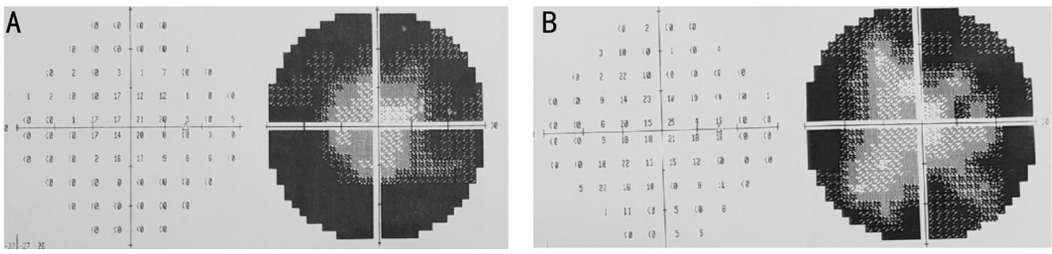

Figure 2 Perimetry results of a patient before treatment (A) and 6mo after treatment (B) Peripheral visual field defect decreased during the study period.

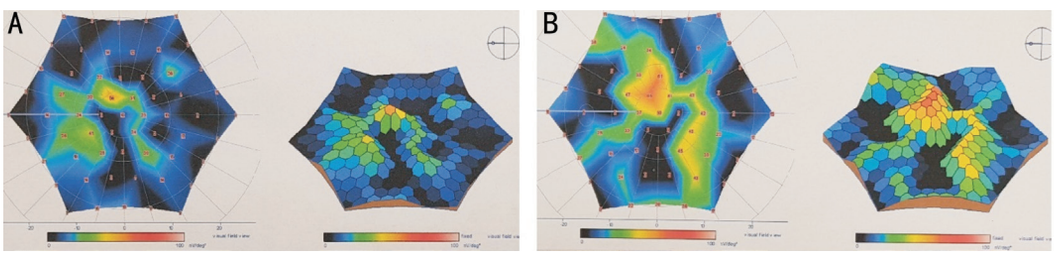

Figure 3 mfERG recording of the same patient before treatment (A) and 6mo after treatment (B) The improvements in mfERG recordings especially in the central rings shown with the color maps and 3D visualization maps.

amount in the current study. Each eye received 5 million UC-MSCs during the surgery.

Postoperative Follow-up Patients were recommended to use topical antibiotic and steroid eye drops four times a day for 1mo after surgery. Routine ophthalmic evaluations, color fundus photographs and OCT were performed before surgery, and at the postoperative 1st day, 1st week, 1st, 3rd, and 6th months. We also performed VF at 1st, 3rd, and 6th months, FFA and mfERG at 6th month postoperatively. All patients were evaluated for adverse events of the surgical procedures during the study period.

Statistical Analysis Statistical analyses were done using SPSS version 20 statistical package program (IBM Corp. in Armonk, NY, USA). Descriptive data are reported as median with interquartile range for non-normally distributed numerical variables, and as the frequencies and percentage for categorical variables. Shapiro-Wilk and Kolmogorov-Smirnov tests were used to assess the distribution of the numeric data. The Related-Samples Friedman's Two-Way Analysis of Variance by Ranks test was used for comparing the VF and BCVA measurements and the Wilcoxon signed-rank test with a Bonferroni correction was conducted for post-hoc pairwise comparison. mfERG measurements were compared using the Wilcoxon signed-rank test. $P<0.05$ was considered as statistically significant level.

RESULTS

One hundred and twenty-four eyes of 82 patients completed 6-month study period. The median age was 38.5y (range between 34 and 46y) and 61.0% of the study group were males. Left eye was operated in 17 (20.8%), right eye was operated in 23 (28.0%) of the patients. Forty-two (51.2%) patients received the treatment for both eyes (Table 1).

Table 1 Demographics of the patients *n*=82

Characteristics	Values
Age (y), median (IQR)	38.5 (34.0-46.0)
Sex (male), *n* (%)	50 (61.0)
Operated eye side, *n* (%)	
OS	17 (20.8)
OD	23 (28.0)
OU	42 (51.2)

IQR: Inter-quartile range; OS: Oculus sinister; OD: Oculus dexter; OU: Oculus uterque.

There were statistically significant improvements in BCVA and VF results during the follow-up (both $P<0.05$). In the pairwise comparison, there were statistically significant improvements in VF and BCVA at the first-month evaluation (both $P<0.05$) and at the sixth-month evaluation (both $P<0.05$) when compared to baseline recordings (Table 2; Figure 2). When we evaluate the BCVA results individually, 57 eyes (46%) experienced an improvement in vision, 52 eyes (42%) remained stable, and 15 eyes (12%) worsened during the follow-up period.

Regarding to the mfERG test, the results of 85 eyes were included in the analysis because of the poor fixation and the artifacts produced in the test results of 39 eyes of 25 patients. The amplitudes of P1 waves in the central rings (<2° and 2°-5° rings) improved significantly at the postoperative 6th month. Besides, the amplitudes of the peripheral rings (5°-10°, 10°-15°, and >15° rings) decreased slightly when compared to preoperative results which were not statistically significant (Table 3; Figure 3). There were also statistically significant improvements in implicit times of P1 waves in central areas (<2°, 2°-5°, and 5°-10° rings) postoperatively. The implicit

Table 2 Comparison of BCVA and VF findings mean±SD

Outcomes	Preop.	Postop. 1st month	Postop. 6th month	P^a
BCVA (logMAR)	1.36±0.64	1.16±0.63	1.09±0.60	<0.05
VF (dB)	28.12±3.18	26.17±4.21	24.19±3.23	<0.05

BCVA: Best corrected visual acuity; SD: Standard deviation; VF: Visual field; dB: Decibel. [a]Related-samples Friedman's two-way analysis of variance by ranks test was used.

times of P1 waves in peripheral rings (10°-15° and >15° rings) did not differ after stem cell implantation (Table 4).

All patients who underwent stem cell treatment revealed no pathology on FFA. We found no morphological changes in OCT scans of the both eyes of the patients. The mean central macular thickness measurements of the all treated eyes did not show any significant changes after treatment.

There were no serious ocular adverse events during the study period. One patient complained about transient vision loss in the treated eye which last for a few minutes at the third day of the surgery. We examined the patient after the event on the same day. Ocular examination including OCT, VF, mfERG and FFA tests were similar to the preoperative tests. Systemic and neurogical evaluation of the patient including MRI and MRI angiography were within normal limits. The patient experienced a slight detoriation in the VF test at the 1st month which recovered at the 6mo visit.

DISCUSSION

Low vision is known to complicate daily life, and chronic visual detoriation caused by retinal disorders have been shown to affect quality of life[20]. Degenerative retinal diseases have no curative treatment to date, however many options are being investigated including gene therapies and cell therapies. Stem cell based treatment modalities are rising in trend and giving hope for reversing the cell death or damage; or at least causing the functional enhancement of the remaining viable cells. Stem cell therapy has been used recently in various ophthalmic diseases which mainly includes hereditary/age related retinal disorders and optic neuropathies and has been shown to have promising results[12,15-19,21-24].

Various sources of stem cells including MSCs have been investigated which are all capable of self-renewal and show multipotency. Peripheral blood, umblical cord, bone marrow, and adipose tissue are the main sources of MSCs. These cells have the advantage of immunosuppressant function and the inhibition of the release of proinflammatory cytokines which also allow for both autologous and allogeneic transplantation, hence do not require immunosupression[2,9]. UC-MSCs have favorable advantageous features to other MSC types such as tissue compatibility, rapid proliferation, high paracrine, and immunomodulatory effect and non tumoral side effect[10,12,25]. In this current study, the researchers preferred to use UC-MSCs due to mentioned advantages above.

Table 3 Comparison of mfERG amplitudes of P1 waves *n*=85 eyes

Ring	Amplitude of P1 wave (nV)	
	Preop.	Postop. 6th month
<2°		
Median (IQR)	265.0 (196.5-475.5)	293.0 (209.0-484.5)[a]
Mean±SD	340.7±197.4	361.8±217.6[a]
2°-5°		
Median (IQR)	139.0 (108.5-244.0)	156.0 (112.0-239.5)[a]
Mean±SD	196.7±138.7	209.3±151.1[a]
5°-10°		
Median (IQR)	83.0 (67.0-116.0)	76.0 (63.5-114.5)
Mean±SD	115.3±84.8	111.8±98.0
10°-15°		
Median (IQR)	63.0 (50.0-78.5)	54.0 (45.0-74.0)
Mean±SD	77.9±51.0	73.1±49.7
>15°		
Median (IQR)	42.0 (33.0-64.0)	35.0 (29.0-50.5)
Mean±SD	52.9±38.9	46.6±31.9

mfERG: Multifocal electroretinogram; SD: Standard deviation; IQR: Interquartile range. Wilcoxon signed-rank test was used. [a]The amplitudes of P1 waves in the central rings (<2° and 2°-5° rings) improved significantly.

Table 4 Comparison of mfERG implicit times of P1 waves *n*=85 eyes

Ring	Implicit time of P1 wave (ms)	
	Preop.	Postop. 6th month
<2°		
Median (IQR)	51.0 (46.9-56.8)	47.8 (43.2-52.4)[a]
Mean±SD	52.7±7.7	49.5±9.0[a]
2°-5°		
Median (IQR)	51.2 (46.7-56.4)	47.3 (43.2-53.2)[a]
Mean±SD	52.8±7.8	49.3±9.6[a]
5°-10°		
Median (IQR)	52.4 (45.9-56.7)	49.2 (45.0-55.5)[a]
Mean±SD	52.3±7.7	50.7±8.7[a]
10°-15°		
Median (IQR)	48.9 (46.4-56.8)	49.8 (46.7-56.7)
Mean±SD	51.5±7.4	51.3±8.7
>15°		
Median (IQR)	49.1 (47.1-56.1)	49.5 (47.7-54.5)
Mean±SD	51.3±7.3	51.6±6.8

mfERG: Multifocal electroretinogram; SD: Standard deviation; IQR: Interquartile range. Wilcoxon signed-rank test was used. [a]There were statistically significant improvements in implicit times of P1 waves in central areas (<2°, 2°-5°, and 5°-10° rings) postoperatively.

The visual symptoms of RP indicate that two types of photoreceptors are affected and degenerated; rods, which mediate achromatic night vision, followed by the tightly packed cones, are essential for high acuity night vision[3]. There are several theories that attempt to explain the secondary death of the cones in RP. These theories are lack of trophic factors produced by rods, oxidative stress, and pro-inflammatory microglial activation, nutrient shortage[1,3]. The lack of GFs in the microenvironment of photoreceptors force the cells to enter into a sleep mode which is also known as dormant phase. If the condition persists this phase is followed by apoptosis and death of the retinal cells. Secretion of the GFs (neural and angiogenic GFs and other neurotrophic factors) from stem cells to the microenvironment decreased the degeneration of retinal cells and prevented the progression of the disease in clinical and preclinical studies[2,9].

Recent clinical studies including stem cell treatments for retinal diseases reported no serious adverse effects[12,17,21,26]. Reticell study investigated the effect of intravitreally implanted MSCs to the quality of life of RP patients[26]. They reported an improvement at the third month visit which returned to the baseline values by month 12.

The Stem Cell Ophthalmology Treatment Study (SCOTS), which is the biggest ophthalmology stem cell clinical trial registered to the 'clinicaltrials.gov' reported results of 17 RP patients. Thirty-three eyes received treatment with SCOTS protocol. Visual acuity improved in 15 eyes (45%), remained stable in 15 eyes (45%), and worsened in 3 eyes (10%) during the 6mo follow-up[21]. Our results were similar to the results of this trial regarding to the visual acuity with an improvement in 46% of eyes, stabilization in 42%, and worsening in 12%.

In another study, the results of subretinal MSCs implantation in 11 advanced stage RP patients were reported. The researchers found an improvement in visual acuity only in one patient which was supported by VF and ERG[5]. First year results of the same study[6] included 14 patients with severe RP. The patients received subretinal MSCs after total vitrectomy. Although there were no systemic complications reported in this study, 6 patients experienced ocular complications. Choroidal neovascular membrane developed in one of the patients which was treated with intravitreal anti-VEGF injections. The first operated six patients had epiretinal membrane with peripheral tractional retinal detachment and received second vitrectomy. Those complications were considered to be secondary to the vitreal reflux or unintended preretinal injection and undesirable proliferation of MSCs, or the already underlying vitreous abnormalities existing in patients with advanced stage RP causing difficulties in removing posterior vitreous. After a modification of the operation technique, epiretinal membrane formation was inhibited in all of the remaining 8 patients. Mild band keratopathy was found in one of the patients at six month visit and retrolental fibrous tissue formation was detected in another patient at 12-month follow-up examination. Four patients showed visual acuity gain during the first year of this study. Authors reported that subretinal transplantation of MSCs may have some side effects and should be applied carefully[6]. Suprachoroidal, subtenon or peribulbar implantation techniques are found to be safe with no serious ocular adverse effects[12,15-19,21-24]. In this current study, UC-MSC implantation was performed to the suprachoroidal space and no serious ocular adverse effects were reported in this large clinical case series. To the best of our knowledge this is the largest stem cell study in the literature including 124 eyes of 82 RP patients. Suprachoroidal delivery method being near the choroid also has the advantage of allowing the produced GFs to enter the choroidal flow and managing the consant GF secretion to the choroidal and retinal tissues. This method has been first introduced by Limoli *et al*[15-17] and was proven to be safe with no complications.

In our study we did not observe any serious ocular complication except a transient vision loss in the treated eye of one patient which last for a few minutes at the third day of the surgery. Ocular examination of the patient including OCT, VF, mfERG, and FFA tests were similar to the preoperative tests. Systemic and neurogical examinations including blood tests, MRI, and MRI angiography showed no pathology. The patient experienced a slight detoriation in the VF test at the first month evaluation which recovered at the sixth month visit. This adverse event was interpreted as an ischemic process by Stem Cell Committee of our hospital, which may or may not be related to the stem cell implantation.

To the best of our knowledge there is only one clinical study in the literature regarding umbilical tissue derived MSC application in RP. In this recent phase 3 study, Özmert and Arslan[12] implanted Wharton's jelly derived MSCs to the subtenon space in 32 RP patients. They observed a significant improvement in the mean BCVA of the patients which increased from 70.5 letters to 80.6 letters at the 6th month. They also found significant improvements in the mean deviation values of VF tests and mean outer retinal thickness measurements. mfERG evaluations of this study demonstrated significant increases in the mean amplitudes and implicit times of P1 waves in the central rings 1, 2, and 3. They also reported improvements in the measurements of full-field flicker electroretinography. The authors concluded that the photoreceptors in peripheral zone may have undergone apoptosis course, but the photoreceptors in central zone were still in the dormant phase and not completed the apoptosis phase. No ocular or systemic side effects were observed related to the Wharton's jelly derived MSC implantation during

the follow-up period in this study[12]. In this current study of ours, UC-MSCs implantation to the suprachoroidal space demonstrated a positive effect on BCVA, VF, and mfERG measurements similar to the results of Özmert and Arslan[12]. The similarity of our results with the literature reinforces the efficacy and safety profile of UC-MSC implantation therapy.

It is known that stem cell based therapies work better when there is more viable tissue and so with patients having more residual visual capacity. It is shown that retinal thickness average (RTA) measurements serve as a diagnostic criterion for stem cell application treatments and better outcomes are revealed in patients with thicker RTA measurements[15-17]. The neuroenhancement which is improved by GFs is proportional to the areas present of greater cellularity which also corresponds with electrophysiology. In a very recent study, Limoli *et al*[17] treated 21 eyes of 15 RP patients with autologous adipose tissue derived MSCs and platelet-rich plasma implanted into the suprachoroideal space and found that the group with a foveal thickness greater than 190 μm is ascoiated with a better prognosis. Considering the late stage spectrum of the patients in our study, regarding to the age and BCVA, the GFs and receptor interaction would be poor and therefore could not represent the potential response that would be received from the patients in early-moderate stages of the disease. Even with this fact the results of our study, despite the heterogeneity of the recruited subjects is promising with no serious complications and gives hope for studies of patients with the beginning/medium phase of their disease.

Limitations These are the limitations of our study. 1) The follow-up period in our study is 6mo and it is not enough to determine how long the obtained improvements in visual function will persist and when a booster treatment will be required. Long term results will be necessary to evaluate the durability of the treatment. 2) This study does not provide data on subjects aged less than 34y or subjects who's having early stage of disease with better visual functions. Thus we do not generalize our findings to the patients with early stage of disease, which their photoreceptors in the periphery are in the dormant phase. 3) Genetic analysis is not included in this study. We believe that genetic testing may guide us to understand the response to the stem cell treatment in different genetic mutations. 4) Though, visual field testing is a sensitive tool to measure the preserved central VF, it has some limitations. The test is a subjective, behavioral method and relies on the patient's cooperation and experience with the test. A more objective test such as microperimetry should be more reliable to evaluate the central VF. 5) This study does not include patients with early phase of RP. Studies comparing different stages of the disease with larger number of patients will help us to identify who will benefit most from stem cell implantations.

In conclusion, RP is a hereditary retinal disease which can cause total blindness with a degeneration process. Currently, the injection of GFs, gene therapy, and cell-based treatments compose the therapeutic options of patients with RP. Regardless of the type of genetic mutation, with respect to the clinical experiences, stem cell treatment based on the use of GFs seems remarkable because they can improve the electrical cell response for a certain period of time. It is expected to observe a greater effect if MSCs therapy can be performed as early as possible during the course of the disease, when most of the photoreceptors are still alive or present. Ongoing observation will yield additional information about the sustained effectiveness of MSCs therapy and the long-term safety.

ACKNOWLEDGEMENTS

We would like to thank Prof. Dr. Ercument Ovalı and the staff members of Acibadem Labcell for providing the stem cells. We also thank to the staff members of Acibadem Kayseri Hospital for their contribution to the study tests.

Authors' contributions: Oner A: Study design, patient management, surgical intervention, manuscript preparation; Kahraman NS: Patient management, data collection, manuscript preparation. All authors read and approved the manuscript.

Conflicts of Interest: Kahraman NS, None; **Oner A,** None.

REFERENCES

1 Smith LE. Bone marrow-derived stem cells preserve cone vision in retinitis pigmentosa. *J Clin Invest* 2004;114(6):755-757.

2 Öner A. Stem cell treatment in retinal diseases: recent developments. *Turk J Ophthalmol* 2018;48(1):33-38.

3 Narayan DS, Wood JP, Chidlow G, Casson RJ. A review of the mechanisms of cone degeneration in retinitis pigmentosa. *Acta Ophthalmol* 2016;94(8):748-754.

4 Berson EL. Retinitis pigmentosa. The Friedenwald Lecture. *Invest Ophthalmol Vis Sci* 1993;34(5):1659-1676.

5 Oner A, Gonen ZB, Sinim N, Cetin M, Ozkul Y. Subretinal adipose tissue-derived mesenchymal stem cell implantation in advanced stage retinitis pigmentosa: a phase I clinical safety study. *Stem Cell Res Ther* 2016;7(1):178.

6 Oner A, Gonen ZB, Sevim DG, Sinim N, Cetin M, Ozkul Y. First-Year results of subretinal mesenchymal stem cell implantation in severe retinitis pigmentosa. *J Stem Cell Res Ther* 2019;9:454.

7 Sharma R, Bose D, Maminishkis A, Bharti K. Retinal pigment epithelium replacement therapy for age-related macular degeneration: are we there yet? *Annu Rev Pharmacol Toxicol* 2020;60:553-572.

8 Fuhrmann S, Zou CJ, Levine EM. Retinal pigment epithelium development, plasticity, and tissue homeostasis. *Exp Eye Res* 2014;123: 141-150.

9 Zarbin M. Cell-based therapy for degenerative retinal disease. *Trends Mol Med* 2016;22(2):115-134.

10 Zhang W, Wang YX, Kong JH, Dong M, Duan HT, Chen S. Therapeutic efficacy of neural stem cells originating from umbilical cord-derived mesenchymal stem cells in diabetic retinopathy. *Sci Rep* 2017;7(1):408.

11 Huo DM, Dong FT, Yu WH, Gao F. Differentiation of mesenchymal stem cell in the microenviroment of retinitis pigmentosa. *Int J Ophthalmol* 2010;3(3):216-219.

12 Özmert E, Arslan U. Management of retinitis pigmentosa by Wharton's jelly derived mesenchymal stem cells: preliminary clinical results. *Stem Cell Res Ther* 2020;11(1):25.

13 Dias MF, Joo K, Kemp JA, Fialho SL, da Silva Cunha A Jr, Woo SJ, Kwon YJ. Molecular genetics and emerging therapies for retinitis pigmentosa: basic research and clinical perspectives. *Prog Retin Eye Res* 2018;63:107-131.

14 Hood DC, Bach M, Brigell M, Keating D, Kondo M, Lyons JS, Marmor MF, McCulloch DL, Palmowski-Wolfe AM, International Society For Clinical Electrophysiology of Vision. ISCEV standard for clinical multifocal electroretinography (mfERG) (2011 edition). *Doc Ophthalmol* 2012;124(1):1-13.

15 Limoli PG, Limoli C, Vingolo EM, Scalinci SZ, Nebbioso M. Cell surgery and growth factors in dry age-related macular degeneration: visual prognosis and morphological study. *Oncotarget* 2016;7(30):46913-46923.

16 Limoli PG, Vingolo EM, Morales MU, Nebbioso M, Limoli C. Preliminary study on electrophysiological changes after cellular autograft in age-related macular degeneration. *Medicine (Baltimore)* 2014;93(29):e355.

17 Limoli PG, Vingolo EM, Limoli C, Nebbioso M. Stem cell surgery and growth factors in retinitis pigmentosa patients: pilot study after literature review. *Biomedicines* 2019;7(4):E94.

18 Oner A, Gonen ZB, Sevim DG, Smim Kahraman N, Unlu M. Suprachoroidal adipose tissue-derived mesenchymal stem cell implantation in patients with dry-type age-related macular degeneration and stargardt's macular dystrophy: 6-month follow-up results of a phase 2 study. *Cell Reprogram* 2018;20(6):329-336.

19 Oner A, Gonen ZB, Sevim DG, Sinim Kahraman N, Unlu M. Six-month results of suprachoroidal adipose tissue-derived mesenchymal stem cell implantation in patients with optic atrophy: a phase 1/2 study. *Int Ophthalmol* 2019;39(12):2913-2922.

20 Kahraman NS, Sevim DG, Öner A. Cross-validation of the Turkish version of the 28-item impact of vision impairment profile test. *OJOph* 2019;9(4):194-202.

21 Weiss JN, Levy S. Stem Cell Ophthalmology Treatment Study: bone marrow derived stem cells in the treatment of retinitis pigmentosa. *Stem Cell Investig* 2018;5:18.

22 Weiss JN, Levy S, Benes SC. Stem Cell Ophthalmology Treatment Study: bone marrow derived stem cells in the treatment of non-arteritic ischemic optic neuropathy (NAION). *Stem Cell Investig* 2017;4:94.

23 Weiss JN, Levy S, Benes SC. Stem Cell Ophthalmology Treatment Study (SCOTS) for retinal and optic nerve diseases: a case report of improvement in relapsing auto-immune optic neuropathy. *Neural Regen Res* 2015;10(9):1507-1515.

24 Weiss JN, Levy S, Benes SC. Stem Cell Ophthalmology Treatment Study (SCOTS): bone marrow-derived stem cells in the treatment of Leber's hereditary optic neuropathy. *Neural Regen Res* 2016;11(10):1685-1694.

25 Ozkan S, Isildar B, Oncul M, Baslar Z, Kaleli S, Koyuturk M. Ultrastructural analysis of human umbilical cord derived MSCs at undifferentiated stage and during osteogenic and adipogenic differentiation. *Ultrastruct Pathol* 2018;42(3):199-210.

26 Siqueira RC, Messias A, Messias K, Arcieri RS, Ruiz MA, Souza NF, Martins LC, Jorge R. Quality of life in patients with retinitis pigmentosa submitted to intravitreal use of bone marrow-derived stem cells (Reticell-clinical trial). *Stem Cell Res Ther* 2015;6:29.