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ORIGINAL PAPER

Six-month results of suprachoroidal adipose tissue-derived mesenchymal stem cell implantation in patients with optic atrophy: a phase 1/2 study

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Abstract

Purpose This prospective clinical case series aimed to investigate the safety and efficacy of suprachoroidal adipose tissue-derived mesenchymal stem cell (ADMSC) implantation in patients with optic nerve diseases.

Methods This prospective, single-center, phase 1/2 study enrolled 4 eyes of 4 patients with optic atrophy of various reasons who underwent suprachoroidal implantation of ADMSCs. The best-corrected visual acuity (BCVA) in the study was HM at 1 m. The worse eye of the patient was operated. Patients were evaluated on the first day, first week, first month, third and sixth months postoperatively. BCVA, anterior segment and fundus examination, color photography, optical coherence tomography (OCT) and visual field examination were carried out at each visit. Fundus fluorescein angiography and multifocal electroretinography (mfERG) recordings were performed at the end of the first, third and sixth months and anytime if necessary during the follow-up.

Results All 4 patients completed the six-month follow-up. None of them had any systemic or ocular complications. All of the patients experienced visual acuity improvement, visual field improvement and improvement in the mfERG recordings. We found choroidal thickening in OCT of the 4 patients.

Conclusion Even though the sample size is small, the improvements were still encouraging. Stem cell treatment with suprachoroidal implantation of ADMSCs seems to be safe and effective in the treatment for optic nerve diseases that currently have no curative treatment options.

Keywords Adipose tissue-derived mesenchymal stem cell · Optic nerve disease · Suprachoroidal implantation

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Introduction

Optic nerve consists of axons of retinal ganglion cells (RGCs) which is the part of the central nervous system. Optic nerve dysfunction and consequent visual loss are caused by various reasons including compression, ischemia, inflammation, trauma and hereditary neuronal and mitochondrial diseases. Loss of RGCs is irreversible and currently lacks a definitive treatment strategy. After it was shown that the death of the RGCs was mainly caused by the decrease in neurotrophic factors in their microenvironment, exogenous supplement of these factors has been tried with target of improving the survival of RGCs; however, it proved to be instable [1–3]. Intravitreal injections of neurotrophic factors via biodegradable microspheres in an experimental glaucomatous optic neuropathy model achieved an increase in the survival of RGCs and their axons and were offered as a neuroprotective tool [4]. Since then, stem cell transplantation has been proposed in various studies as a new method. Researchers have shown that intravitreal administration of bone marrow-derived mesenchymal stem cells (BMMSCs) could significantly increase the survival rate of RGCs with experimental models through various mechanisms including neurotrophic factors, gene modification, immunoregulation or differentiation into neurons [5].

Non-ocular-derived stem cells include embryonic stem cells (ESCs), induced pluripotent stem cells (IPSCs), mesenchymal stem cells (MSCs) which include bone marrow MSCs (BMMSCs) and adipose-derived MSCs (ADMSCs). When compared to BMMSCs, ADMSCs have the advantages of easier harvest from donors, faster expansion, more protein secretion and higher immunomodulatory capacity [6]. Experimental studies showed that ADMSC implantation can improve the visual function in optic nerve injury models [7, 8]. After the successful results of preclinical studies, human trials including stem cell applications in optic nerve diseases are established.

In this study, our aim was to investigate the safety, efficacy and efficiency of suprachoroidal ADMSC implantation in patients with optic atrophy. To our knowledge, this is the first study in the literature investigating the effects of ADMSCs in patients with optic atrophy.

Methods

This prospective, single-center, phase 1/2 study enrolled 4 eyes of 4 patients with optic atrophy of various reasons (including diabetes pseudotumor cerebri and methanol induced optic neuropathy) who admitted to the Retina and Vitreous Section of the Ophthalmology Department of our medical faculty. In cases of patients where both eyes were eligible to the study, the eye with worse visual acuity was enrolled in the study. Approval by the Institutional Review Board of Medical School of The University (No: 2017/480, date: 13.10.2017) was obtained, and the study was conducted in adherence with the tenets of the Declaration of Helsinki. According to the regulations in our country, approval by the Review Board of Stem Cell Applications of the Ministry of Health was also obtained (Review number for approval: 56733164/203). All the patients were individually instructed on the methodology of the study, and written informed consent was obtained from all individual participants included. The inclusion criteria were as follows: (1) patients older than 18 years (2) a clinical diagnosis of optic atrophy and (3) best-corrected visual acuity (BCVA) of <20/200.

Patients with previous ocular surgery other than cataract extraction, ocular media opacities that would make the image quality not sufficient for ocular imaging or effect the mfERG or visual field evaluation, coexisting ocular disease (i.e., retinal pathology, uveitis, strabismus, nystagmus), any other systemic disease that would affect the results were excluded from the study.

A single experienced vitreoretinal surgeon (AO) performed all the surgical procedures and ophthalmic evaluations. All patients underwent baseline ophthalmic evaluation including baseline BCVA, applanation tonometry, slit lamp biomicroscopy, color fundus photography, optical coherence tomography (OCT), retinal nerve fiber layer (RNFL) analysis, fundus fluorescein angiography (FFA) and multifocal electroretinography (mfERG) recordings. Visual acuity was recorded using a Snellen chart at a distance of 3 m and presented as logarithm of the minimum angle of resolution (logMAR) units. Fundus photography and FFA were performed using the Zeiss FF 450 (Carl Zeiss Meditec AG, Germany). Spectral-domain OCT and RNFL measurements were taken using the Heidelberg OCT device (Heidelberg Engineering,

Heidelberg, Germany) with a standardized scanning protocol and enhanced depth imaging (EDI) mode. Visual field examination was performed by Octopus Goldmann Perimetry (Octopus 900, Haag Streit İnternational, Switzerland). mfERG (Monpack 3, Metrovision, France) readings were recorded from each eye according to the International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines [9].

Surgical technique

Surgeries were all carried out with local anesthesia. We performed a surgical technique defined as Limoli retinal restoration technique (LRRT) which is described by Limoli et al. [10]. Each eye received a cell graft of ADMSCs between choroid and sclera.

The isolation and culture of ADMSCs and their flow cytometry analyses were performed as previously mentioned by our study group [11]. For platelet-rich plasma (PRP) preparation, 8 mL of human peripheral blood was collected in a Regen-BCT tube (RegenKit; RegenLab, Le Mont-sur-Lausanne, CH). The collected blood was centrifuged for 10' at 1500 G.

The details of the surgery are as follows: The globe was deviated to the supero-nasal quadrant, and conjunctiva was dissected at the infero-temporal quadrant at 8 mm from the limbus. A deep scleral flap of about 5 × 5 mm was opened by radial hinge at the infero-temporal quadrant. The sclerectomy was deep enough to allow viewing the color of the choroid. A flap from the orbital fat was extracted from a gap above the inferior oblique muscle. This tissue was laid on the scleral bed and sutured with 6/0 vicryl at the proximal edge. The scleral flap was then sutured above the fat pedicle. The remaining space between the autologous fat graft, choroid and scleral flaps was filled with 1 cc of $2x10^6$ ADMSCs and 1 cc of PRP using a 25-gauge cannula. The conjunctiva was sutured with 8/0 vicryl.

Postoperative follow-up

Patients were hospitalized for 1 day after the surgery and received topical antibiotic and steroid drops four times daily during the first month. Ophthalmic evaluations including BCVA, anterior and posterior segment examination and OCT were performed at day 1, at week 4, and then at months 3 and 6 after the surgery. Color fundus photographs, visual field examination, FFA, RNFL analysis and mfERG recordings were also obtained before surgery and at months 1, 3 and 6 during the follow-up period.

Case presentations

Patient 1

This is a 52-year-old male with diabetes mellitus who had been followed up in our Retina and Vitreous Section for 10 years. He had received bilateral panretinal argon laser photocoagulation for diabetic retinopathy in 2013. The patient had been suffering from progressive vision loss during the last 2 years due to the progressive optic atrophy. His vision decreased from 10/20 to 10/100 in the right eye and from 10/20 to 10/1000 in the left eye. Systemic and neurological examinations including MRI of the patient were normal; therefore, optic neuropathy was considered to be due to diabetes mellitus.

At the examination before stem cell treatment his visual acuities were 10/200 in the right eye and hand motion (HM) at 2 feet in the left eye. Anterior segment evaluation of both eyes was normal. Intraocular pressure measurements were 15 mmHg in both eyes. Optic nerves were pale in both eyes. Visual field examination of the patient showed bilateral central islands which were smaller in the left eye. Bilateral decreased amplitudes were obtained with mfERG recordings. Both OCT and RNFL measurements showed thinning of macula, choroid and nerve fiber layer in both eyes.

The patient underwent stem cell treatment procedure in the left eye without complications. At the examination after 6 months, visual acuity increased to counting fingers (CF) at 2 m the central island in the visual field enlarged as seen in Fig. 1. mfERG recording improved in the treated left eye (Fig. 2). Although macular thickness and RNFL analysis remained unchanged, choroidal thickness increased from 273 to 318 μm (Figs. 3 and 4). There was no pathology in FFA of all patients after the treatment (Fig. 5). No changes in perfusion and no tumors or neovessels were found following the stem cell surgery. Unfortunately, untreated right eye worsened in all examinations.

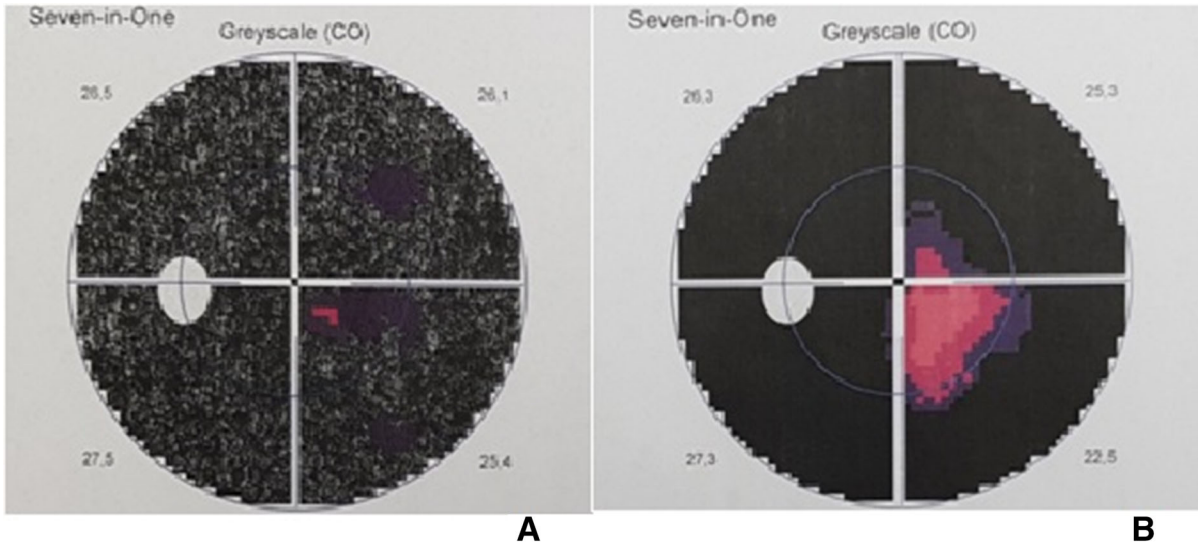

Fig. 1 Visual field examination of patient 1 before treatment (**a**) and after treatment (**b**). Note the enlargement of the central island after treatment

Patient 2

This is a 34-year-old female referred from an outpatient clinic. She had suffered from bilateral sudden visual loss after consuming unbranded alcohol. She was treated in another tertiary center during the acute phase of intoxication. She was examined in our clinic 6 months after methanol intoxication. On presentation, her systemic and neurological examinations were normal. Her visual acuities were only light perception, and her optic nerves were atrophic in both eyes. Visual field examinations were undetectable in both eyes.

The patient underwent stem cell treatment procedure in the left eye without complications. At the examination after 6 months, visual acuity increased to HM at 2 feet. Visual field showed a small central island. Although macular thickness, RNFL scan and FFA remained unchanged, mfERG recording improved and choroidal thickness increased from 223 to 292 μm in the treated left eye. Untreated right eye showed no improvements.

Patient 3

This patient is a 61-year-old male who was under routine follow-up in our Retina and Vitreous Section for 5 years. He had received bilateral panretinal argon laser photocoagulation for diabetic retinopathy in 2015. On his last routine follow-up examination, his visual acuities were 20/25 in both eyes. After consuming unbranded alcohol, he suffered from bilateral progressive visual impairment and his vision decreased to HM at 2 meters in the right eye and 10/100 in the left eye in 3 days. Ophthalmological examination showed edema and hyperemia of both optic disks. Systemic and neurological examinations including MRI of the patient were normal; therefore, optic neuropathy was considered to be due to methanol intoxication. During follow-up examinations, optic disks became atrophic and pale.

At the examination before stem cell treatment his visual acuities were HM at 1 m in the right eye and 10/200 in the left eye. Visual field examination of the patient showed bilateral central islands which were smaller in the right eye. mfERG recordings showed bilateral decreased amplitudes in both eyes. Both OCT and RNFL measurements showed thinning of macula and nerve fiber layer in both eyes.

The patient underwent stem cell treatment procedure in the right eye without complications. At the examination after 6 months, visual acuity increased to counting fingers CF at 2 meters and the central island in the visual field enlarged. Although macular thickness, RNFL scan and FFA remained unchanged, mfERG recording improved and choroidal thickness increased from 208 to 270 μm in the treated left eye. Unfortunately, untreated right eye worsened in all examinations.

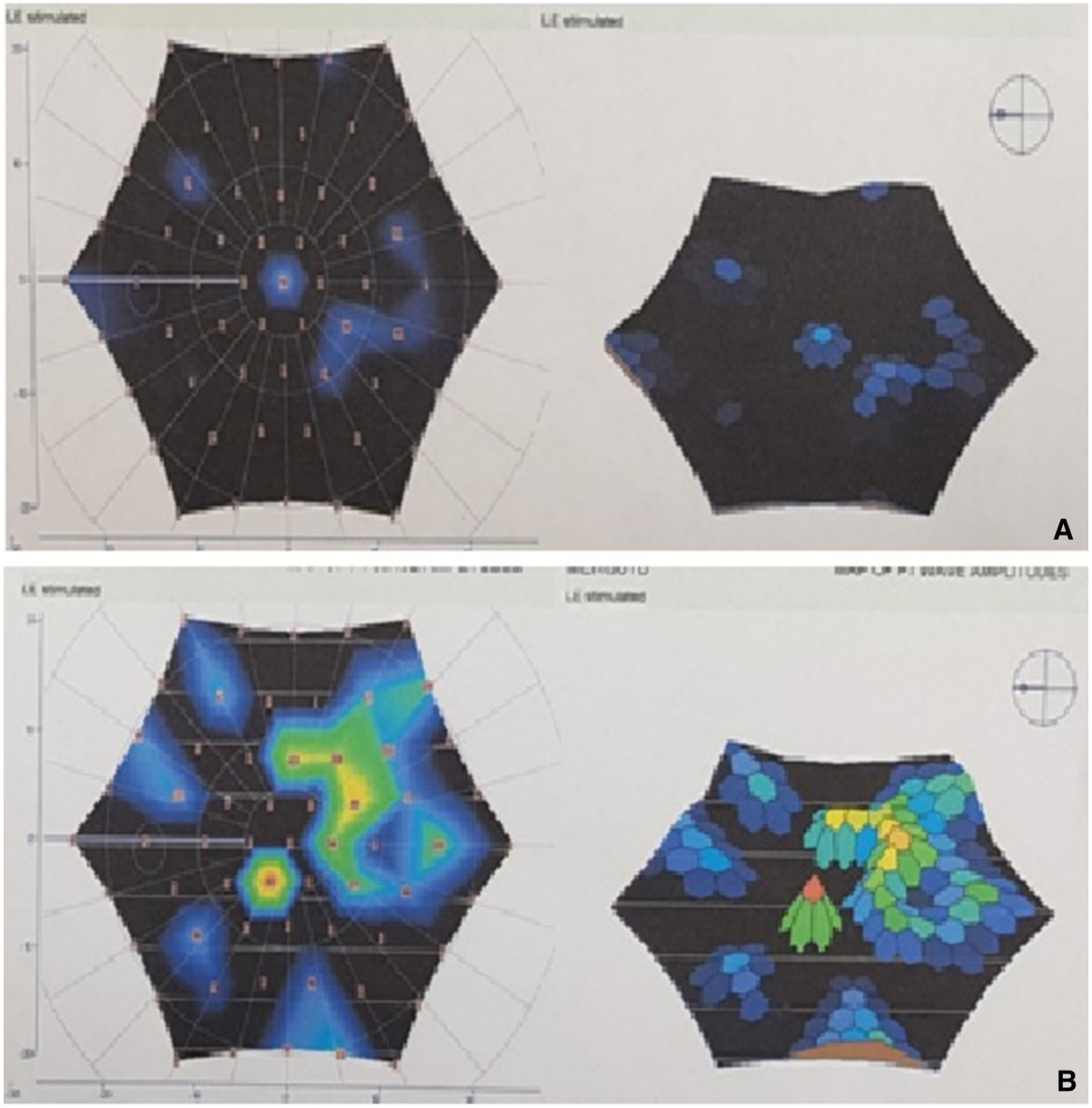

Fig. 2 Multifocal ERG recording of patient 1 before treatment (**a**) and 6 months after treatment (**b**). Note the improvement in 3D visualization map

Patient 4

This patient is a 36-year-old female referred to our clinic from another center. She was diagnosed as pseudotumor cerebri in 2013, and she received medical treatment. At presentation, her visual acuities were HM at 1 m in both eyes and her optic disks were pale. Perimetry of the patient showed bilateral central islands which were smaller in the left eye. mfERG recordings showed bilateral decreased amplitudes in both eyes. Both OCT and RNFL measurements showed thinning of macula and nerve fiber layer in both eyes.

The patient underwent stem cell treatment procedure in the left eye without complications. At the examination after 6 months, visual acuity increased to

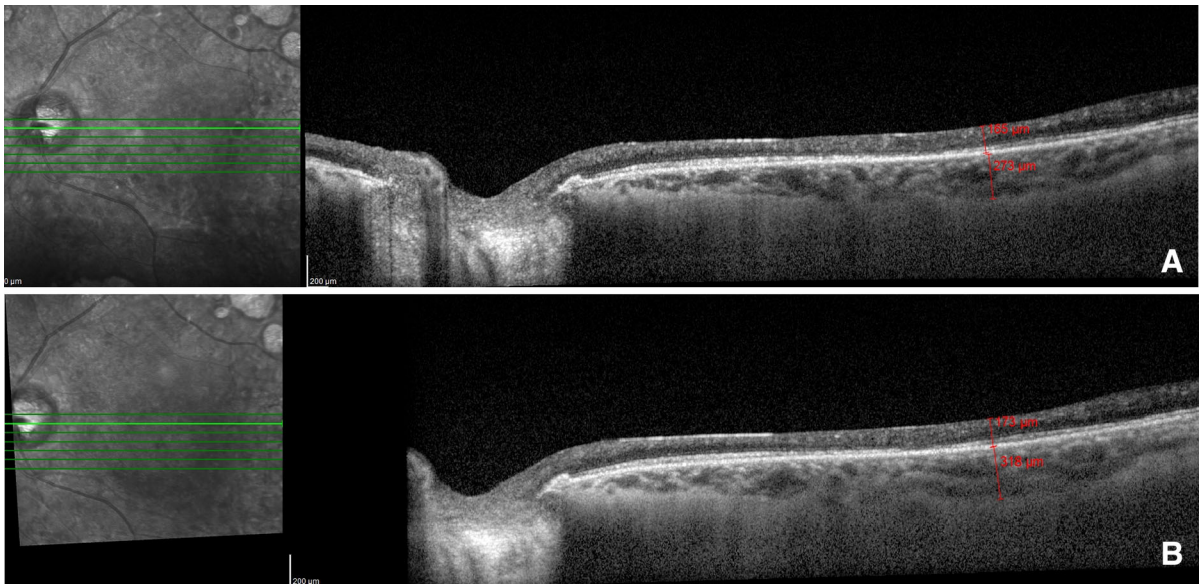

Fig. 3 OCT images of patient 1 before treatment (**a**) and 6 months after treatment (**b**). Choroidal thickness increased from 273 to 318 μm after treatment

counting fingers CF at 2 meters and the central island in the visual field enlarged. Although macular thickness, RNFL scan and FFA remained unchanged, mfERG recording improved and choroidal thickness increased from 261 to 290 μm in the treated left eye. Untreated right eye remained unchanged in all examinations.

Discussion

Since part of the causes for loss of RGCs were shown to be the loss of retrograde neurotrophic transport to the RGC soma, exogenous supplementation of neurotrophic factors to the retina has been offered to promote RGC function and survival. However, blood–retinal barrier and other possible factors make it problematic for these neurotrophic factors to sufficiently reach the retina so that oral supplementation would require very high doses and also topical eye drops. In this manner, local injection of neurotrophic factors into the vitreous has been tried and proved to be beneficial, especially with the combination of a slow-release formulation; still this approach would require frequent injections over a prolonged period and would not be ideal due to its expense, inconvenience and infection risk. Therefore, stem cells provide a more desirable and effective method. Up to date, stem cell differentiation into retinal cell has mostly focused on retinal pigment epithelial and photoreceptor cells, yet it is known that retinal progenitor cells are the first-born cells in the retina during developmental period; current stem cell culture systems for producing cells in the later period should contain RGCs at some point during differentiation [12, 13].

There are numerous experimental studies in the literature suggesting the neuroprotective effects of stem cells in optic nerve diseases [5, 7, 8, 14]. Hu et al [14] showed that intravitreally transplanted BMMSCs protected RGCs from death in an optic nerve injury model. The effect of BMMSCs is thought to be related to expression of nerve growth factors including brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF). Another experimental study investigated the regeneration effects of ADMSCs in optic nerve injury and showed functional improvement in vision responses and suppression of inflammation [8]. The successful results in preclinical studies encourage clinicians to establish clinical trials including stem cell applications in optic nerve diseases.

The first patients were treated within the Stem Cell Ophthalmology Treatment Study (SCOTS) which is the largest ophthalmology stem cell study registered at the National Institutes of Health to date (www.clinicaltrials.gov Identifier NCT: 01920867). One of

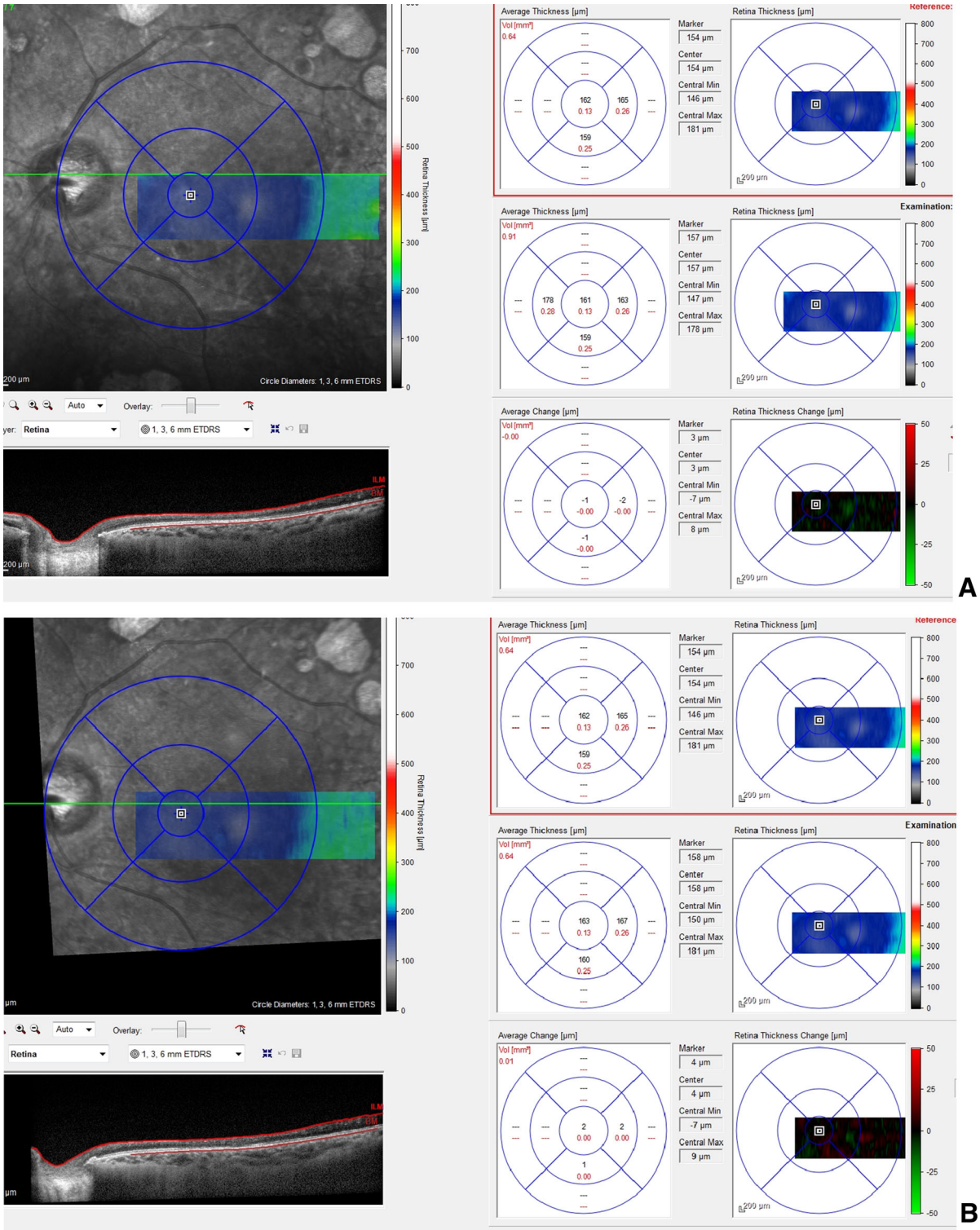

Fig. 4 RNFL scan of patient 1 before (**a**) and after (**b**) treatment. The thickness of the RNFL remained unchanged

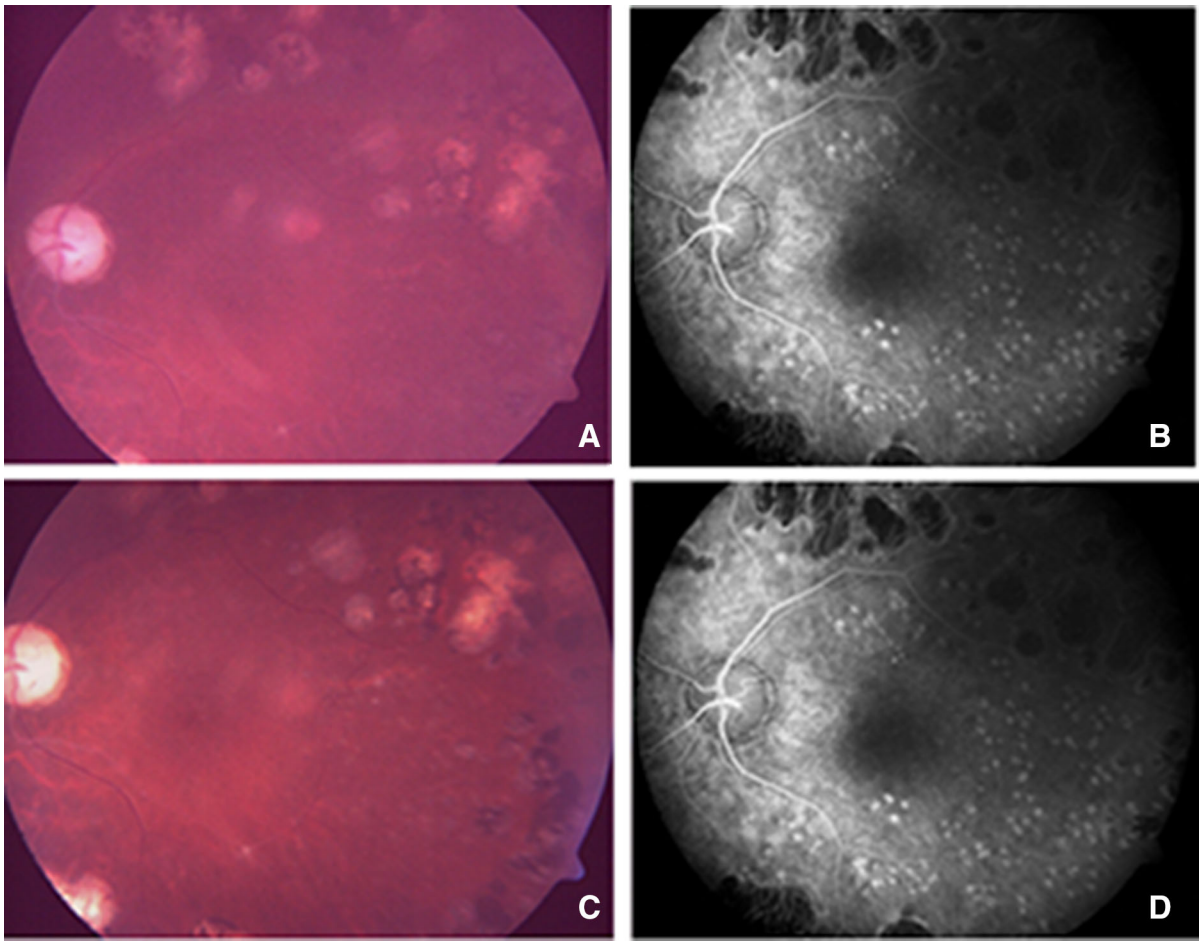

Fig. 5 Color fundus and FFA photographs of patient 1 before (**a**, **b**) and after (**c**, **d**) treatment. Color fundus photographs (**a**, **c**) show pale optic disks and argon laser scars. FFA photographs show hyper- and hypoflourescent areas due to laser scars. There was not a new pathology in FFA after the treatment

these patients was a 54-year-old female patient with decreased vision in both eyes as a consequence of relapsing autoimmune optic neuritis [15]. The patient was submitted to vitrectomy with injection of BMMSCs into the optic nerve of the right eye and retrobulbar, subtenon and intravitreal injections of BMMSCs in the left eye. Improvement in the visual acuity of the both eyes as well as improvement in visual field and OCT parameters was achieved with no major complications during the 15-month follow-up period. Another 27-year-old female with idiopathic bilateral optic neuritis leading to bilateral optic atrophy enrolled in SCOTS also underwent the same procedure, and the outcome was significant improvement in vision in both eyes that remain stable at the 12-month follow-up [16]. In another arm of the SCOTS enrolling patients with Leber's hereditary optic neuropathy (LHON), patients had visual acuity gaining up to 35 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, visual field improvements and thickening of macular and optic nerve head nerve fiber layers with no serious complications [17].

Another recent publication of SCOTS including ten patients with bilateral visual loss due to sequential non-arteritic ischemic optic neuropathy (NAION) showed that 80% of patients experienced visual acuity improvement and 20% remained stable. There was an average of 3.53 Snellen lines of vision improvement per eye, and improvements typically occurred within 6 months of stem cell therapy. It was mentioned that the duration of visual loss did not affect the response to the treatment. The study suggested that possible

mechanisms of the visual improvement may include paracrine secretion of proteins and hormones, transfer of mitochondria release of messenger RNA or other compounds via exosomes or microvesicles and neuronal transdifferentiation of the stem cells [18].

Limoli et al. [10, 19] treated 36 eyes of 25 dry AMD patients with surgically grafted autologous cells, platelets from platelet-rich plasma and ADMSCs to the suprachoroidal space, in order to achieve a constant production of growth factors at the chorioretinal level. The surgical technique was called as LRRT. In the current study, LRRT was used as the stem cell implantation technique with two important elements: neurotrophic GFs from ADMSCs to slow down RPE cells and photoreceptor apoptosis; angiotrophic GFs from ADMSCs and PRP for therapeutic purposes to improve choroidal flow.

Up to date, no standardized treatment modality has been proved including the route of delivery for the stem cells. SCOTS used different routes including retrobulbar, subtenon, intravitreal and intra-optic nerve for stem cell implantation, and they found no differences between results. In the previous study of our group, where we performed subretinal ADMSC implantation to advanced-stage patients with RP, we faced various ocular complications including choroidal neovascular membrane (CNV) at the site of the implantation and epiretinal membrane (ERM) around the transplantation site and at the periphery causing localized peripheral tractional retinal detachment which required second surgeries including vitrectomy and silicon oil injections and led us to the need for modifying the initial technique [11]. Suprachoroidal technique was applied in another study of our group in retinal diseases, and it was found to be safe with no systemic or ocular complications and effective for stem cell implantation [20]. Suprachoroidal approach has the advantage of delivering the tissue to the retina and retina pigment epithelium (RPE), without having to violate the vitreous cavity, therefore reducing the related surgical complications as this technique includes no removal of vitreous and no iatrogenic retinal hole [21].

We know that our study population is small, including patients with poor visual function who are considered as legally blind which limited our ability to perform reliable measurements of visual functions. The limitations of our study were that besides the small sample size, the study was not masked and there were no controls. However, even though none of the patients recovered functional vision, the improvements were still encouraging. In the near-future studies, including large number of patients with better visual acuities will help us to understand the effect of stem cell therapies.

In this study, we applied two important elements to the suprachoroidal area: neurotrophic and angiotrophic GFs from ADMSCs; and angiotrophic GFs from PRP for therapeutic purposes to improve choroidal flow. We found improvement in visual performance, visual field and mfERG recordings and choroidal thickness measurements in the treated eyes at 6-month follow-up. Ocular complications were not observed in any of the patients. We concluded that electrophysiological and anatomical improvements in the treatment group may indicate the therapeutic role of ADMSCs in optic nerve diseases. In conclusion, stem cell-based treatment modalities have been showing promising results in optic nerve diseases that currently have no curative treatment options. We believe that in the near-future stem cell therapies will hold an important place in the treatment for degenerative retinal and optic nerve diseases.

Author contribution All authors have contributed significantly and are in agreement with the content of the manuscript.

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Compliance with ethical standards

Conflict of interest All of the authors declare that they have no conflict of interest.

Ethics approval and consent to participate All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board (Review number for approval: 2017/480, date: 13.10.2017). It was also approved by the Review Board of Stem Cell Applications within the Ministry of Health in accordance with the regulations in our country (Review number for approval: 56733164/203). All patients were instructed about the objectives and methodology of the study and gave written informed consent to participate.

Consent for publication All patients gave written informed consent for publication of images.

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