Delivery of Stem Cells to the retina: research findings and trends

PROF DR AYSE ONER, FEBO et al.

ERCIYES UNIVERSITY

MEDICAL FACULTY

OPHTHALMOLOGY DEPT.

KAYSERI –TURKEY

WHAT IS STEM CELL

- Stem cells are unspecialized cells
- They can give rise to specialized mature cells.
- They are highly proliferative.
- They have the potential to repair tissue and restore function after injury.

Mechanisms of Action

- 1. Cell replacement: Healthy stem cells can replace unhealthy or lost stem cells.
- 2. Nutritional support: Healthy stem cells increase support to surrounding cells by secreting growth factors.
- 3. Anti-apoptosis: Stem cells can regulate the degeneration of retinal cells and vessels by inhibiting apoptosis.
- 4. Synapse formation: They can create new synaptic connections.

NUTRITIONAL SUPPORT

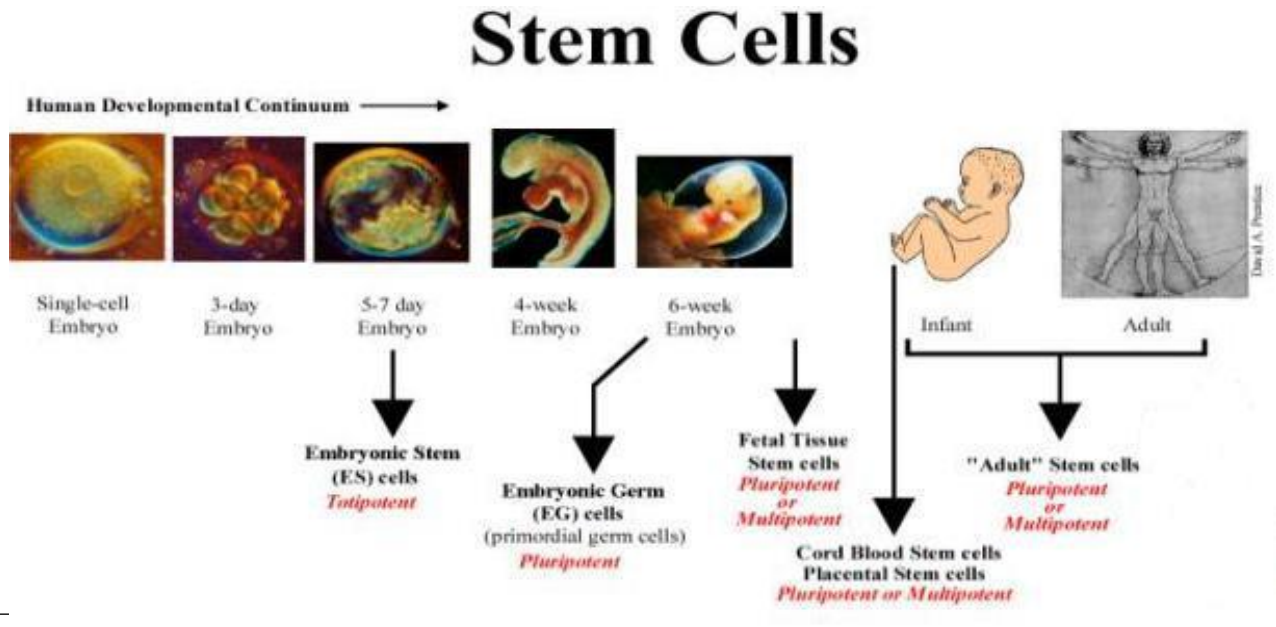
- Stem cells secrete some trophic factors and for the survival of surrounding cells.
- Proangiogenic factors: Angiogenin, PLGF
- Angiogenic chemokines: CXCL1, CXCL,CXCL5,CXCL6 ve CXCL8
- Angiogenic growth factors: HGF, bFGF, VEGF-D, PDGF-AA, TGF-β2, G-CSF, TGF-β2
- Neurotrophic factors: bFGF, nerve growth factor (NGF), neurotrophin 3 (NT3), neurotrophin 4 (NT4), glial-derived neurotrophic factor (GDNF)

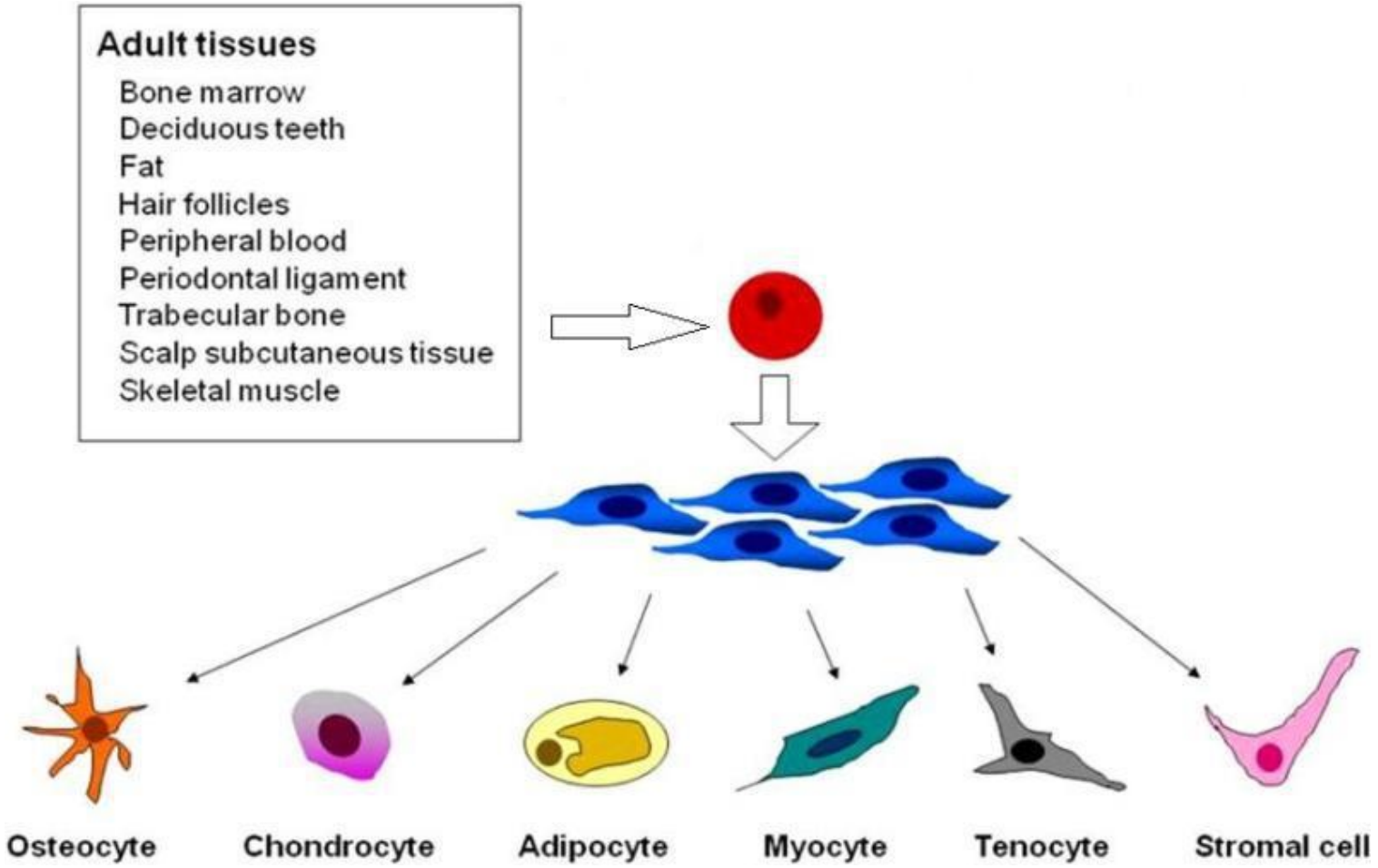
TYPES OF STEM CELLS

1- Embryonic stem cells (ESC)

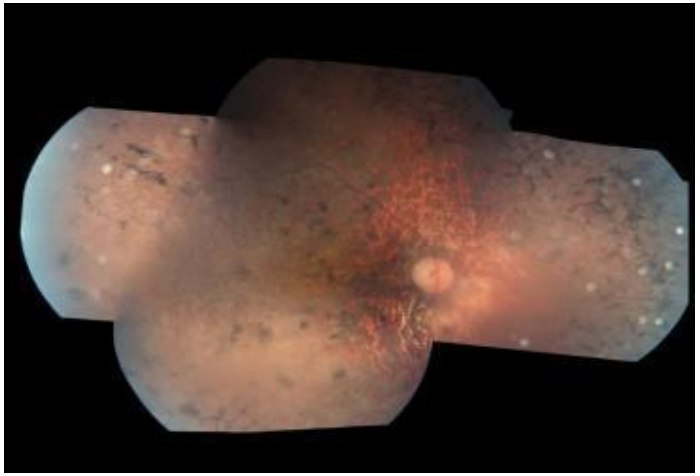
2- Adult Stem Cells

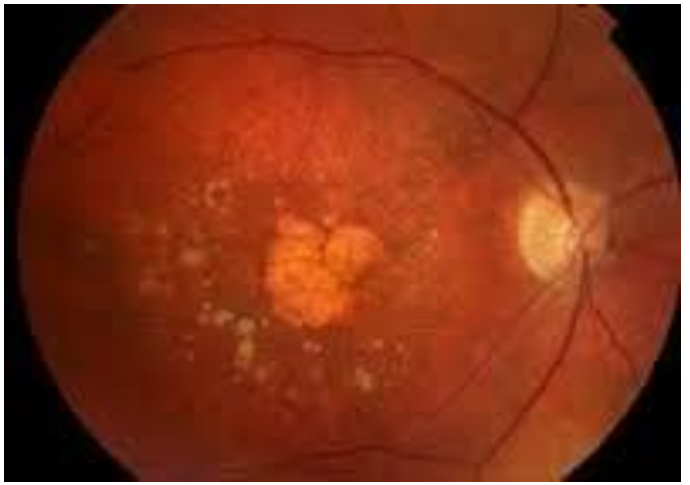
- Mesenchymal Stem Cells (MSC)
  (Adipose Tissue, Bone marrow, Umblical cord)
- Induced pluripotent stem cells (IPSC)



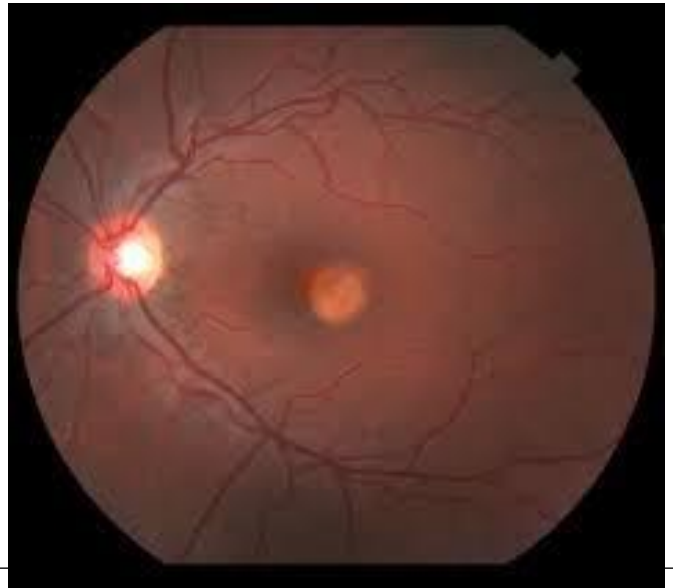

Adult tissues
Bone marrow
Deciduous teeth
Fat
Hair follicles
Peripheral blood
Periodontal ligament
Trabecular bone
Scalp subcutaneous tissue
Skeletal muscle
Osteocyte
Chondrocyte
Adipocyte
Myocyte
Tenocyte
Stromal cell

TARGET DISEASES OF STEM CELL IMPLANTATION





RP, LCA, AMD, BEST, STARGARDTS' OPTIC NERVE DISEASES



Stem Cell And Eye

- There are numerous advantages of stem cell therapy in the eye.
- The amount of stem cells required is low, which is important in terms of cost.
- The surgical approach is quite easy, and the transplanted cells can be easily monitored with the imaging methods.
- The fellow eye can be used as a control.
- Long-term immunosuppressive treatment is not required due to the immune privilege of the eye.

TYPES OF STEM CELLS FOR EYE

- ESCs,
- IPSCs,
- MSCs (bone marrow, adipose tissue and umblical cord tissue)

Surgical Approach For Stem Cell

- 1- Intravitreal
- 2-PPV and Subretinal
- 3- Suprachoroidal
- 4-Retrubulbar/Subtenon
- 5-Intravenous

1- Intravitreal Implantation

Siqueira *et al. Stem Cell Research & Therapy* (2015) 6:29
DOI 10.1186/s13287-015-0020-6

stem cell research&therapy

RESEARCH Open Access

Quality of life in patients with retinitis pigmentosa submitted to intravitreal use of bone marrow-derived stem cells (Reticell -clinical trial)

Rubens C Siqueira[1,2,5*], Andre Messias[1], Katharina Messias[1], Rafael S Arcieri[1], Milton A Ruiz[4], Neiglene F Souza[2], Lia C Martins[3] and Rodrigo Jorge[1]

-MSCs were applied intravitreally to 20 patients who were followed for 1 year.

-The authors reported a statistically significant improvement in the patients' vision related quality of life .

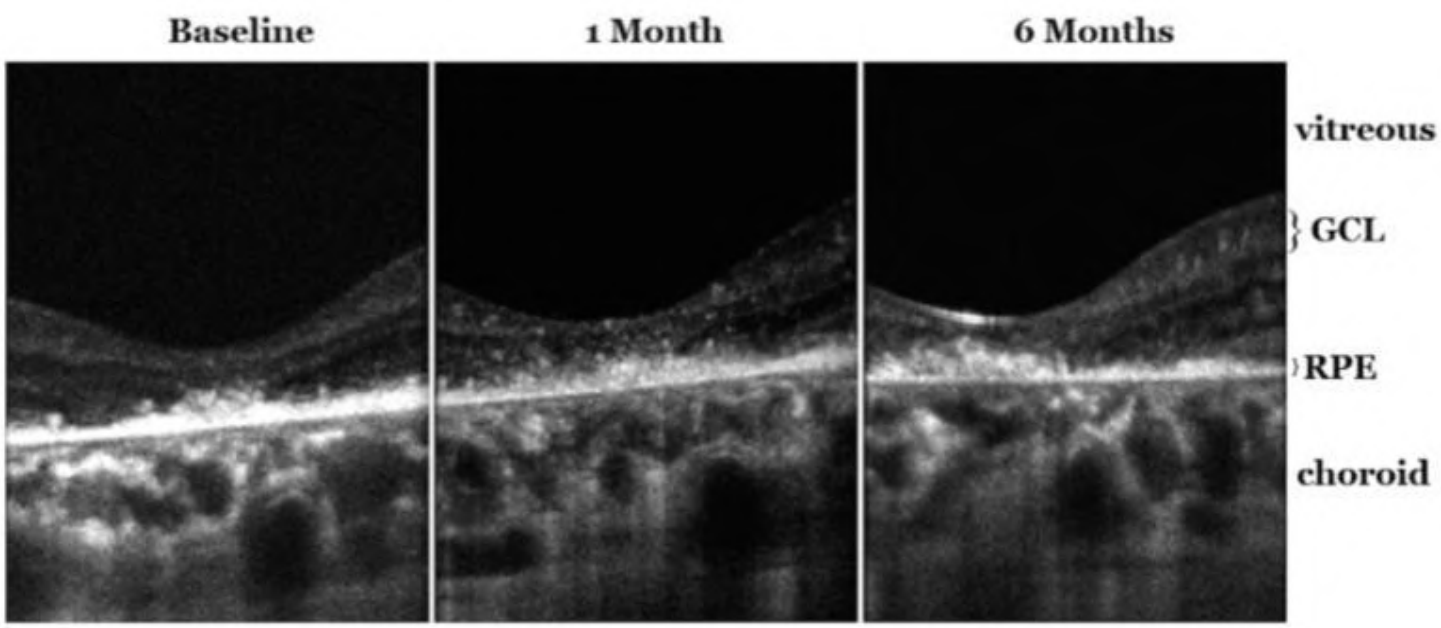
Clinical Trials

Intravitreal Autologous Bone Marrow CD34+ Cell Therapy for Ischemic and Degenerative Retinal Disorders: Preliminary Phase 1 Clinical Trial Findings

Susanna S. Park,[1] Gerhard Bauer,[2] Mehrdad Abedi,[3] Suzanne Pontow,[2] Athanasios Panorgias,[1] Ravi Jonnal,[1] Robert J. Zawadzki,[1] John S. Werner,[1] and Jan Nolta[2]

[1]Department of Ophthalmology and Vision Science, University of California-Davis Eye Center, Sacramento, California, United States
[2]Institute for Regenerative Cures, University of California-Davis School of Medicine, Sacramento, California, United States
[3]Division of Hematology and Oncology, University of California-Davis Cancer Center, Sacramento, California, United States

IOVS- January 2015



Increase in hyperreflectivity on OCT

Original Article

Intravitreal Injection of Bone Marrow Mesenchymal Stem Cells in Patients with Advanced Retinitis Pigmentosa; a Safety Study

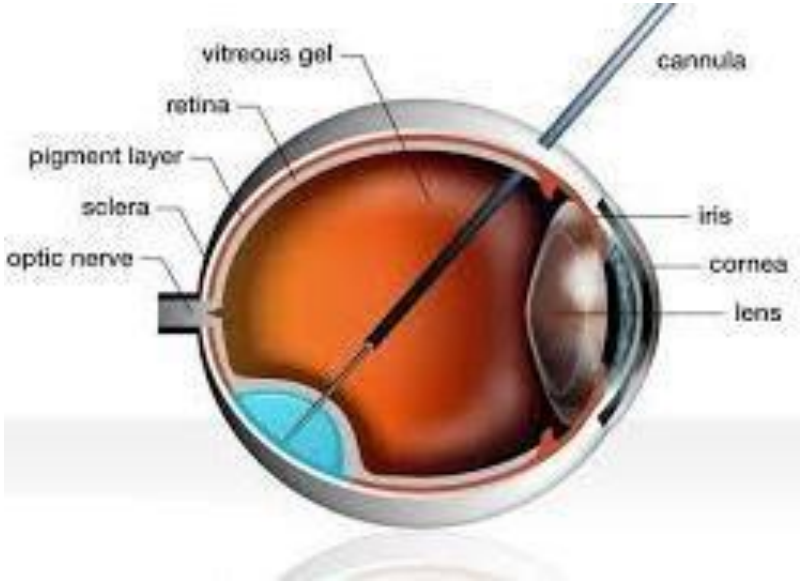
Leila Satarian[1], PhD; Ramin Nourinia[2], MD; Sare Safi[2], MS; Mozhgan Rezaei Kanavi[3], MD
Neda Jarughi[4], MS; Narsis Daftarian[3], MD; Leila Arab[4], MD; Nasser Aghdami[4], MD, PhD; Hamid Ahmadieh[2], MD
Hossein Baharvand[1,4,5], PhD

[1]Department of Stem Cells and Developmental Biology, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran
[2]Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Ocular Tissue Engineering Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Department of Regenerative Medicine, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran
[5]Department of Developmental Biology, University of Science and Culture, ACECR, Tehran, Iran

- Vision improvement and no adverse events were observed in eyes of 2 patients.

- Severe fibrous tissue proliferation, tractional retinal detachment (TRD), iris neovascularization and formation of mature cataract was observed in one patient.

2- SUBRETINAL IMPLANTATION
SC Suspension or SC Sheet



Lancet. 2015 Feb 7;385(9967):509-16. doi: 10.1016/S0140-6736(14)61376-3. Epub 2014 Oct 15.

Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies.

Schwartz SD[1], Regillo CD[2], Lam BL[3], Eliott D[4], Rosenfeld PJ[3], Gregori NZ[3], Hubschman JP[5], Davis JL[3], Heilwell G[5], Spirn M[2], Maguire J[2], Gay R[6], Bateman J[6], Ostrick RM[5], Morris D[6], Vincent M[6], Anglade E[6], Del Priore LV[7], Lanza R[8].

-Subretinal transplantation of hESC-derived RPE

-9 patients with Stargardt's macular dystrophy , 9 patients with atrophic AMD

- Followed up for a median of 22 months

-No serious ocular or systemic safety issues related to the transplanted tissue.

-13 of 18 patients had patches of increasing subretinal pigmentation.

-

-VA improved in 10 eyes, improved or remained the same in 7 eyes, and decreased in 1 eye

Stem Cell Reports
Article
ISSCR
OPEN ACCESS

Treatment of Macular Degeneration Using Embryonic Stem Cell-Derived Retinal Pigment Epithelium: Preliminary Results in Asian Patients

Won Kyung Song,[1,*] Kyung-Mi Park,[2] Hyun-Ju Kim,[2] Jae Ho Lee,[3] Jinjung Choi,[4] So Young Chong,[5] Sung Han Shim,[6] Lucian V. Del Priore,[7] and Robert Lanza[8,*]
[1]Department of Ophthalmology, CHA Bundang Medical Center, CHA University, Seongnam-si, Gyeonggi-do 463-712, Republic of Korea

4 AMD, 4 Stargardt MD cases, 1 year follow-up

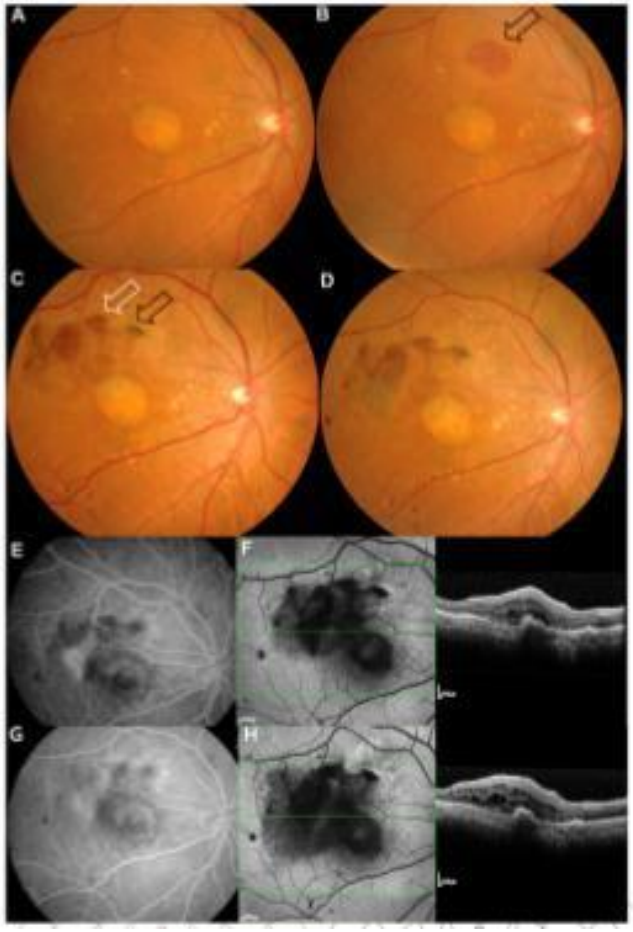
Subretinal hESC-derived RPE

No serious adverse event, no systemic side effect

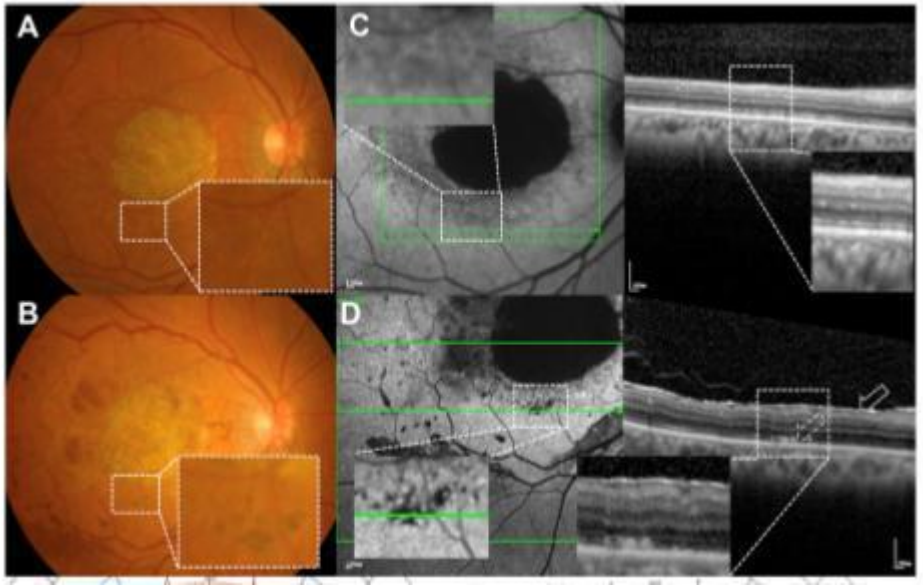
CNVM in one patient , received 3 Lucentis

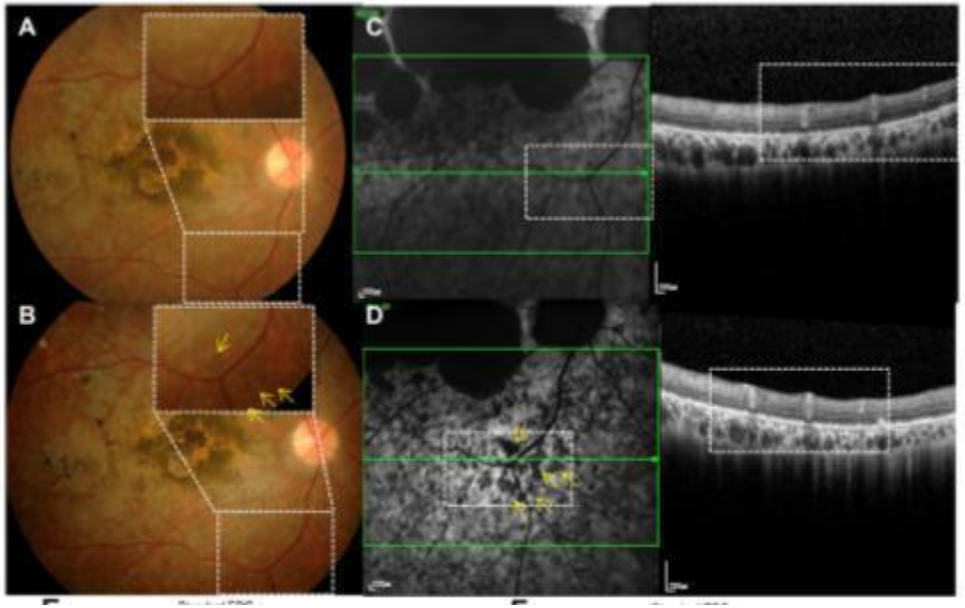
Increase in pigmentation in all cases

VA increase in all cases



CNVM in 1 case





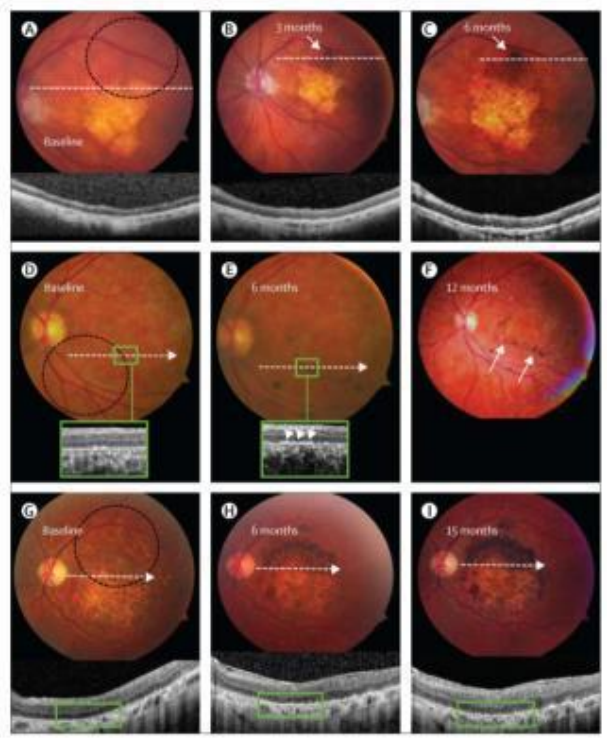
Subretinal pigmentation

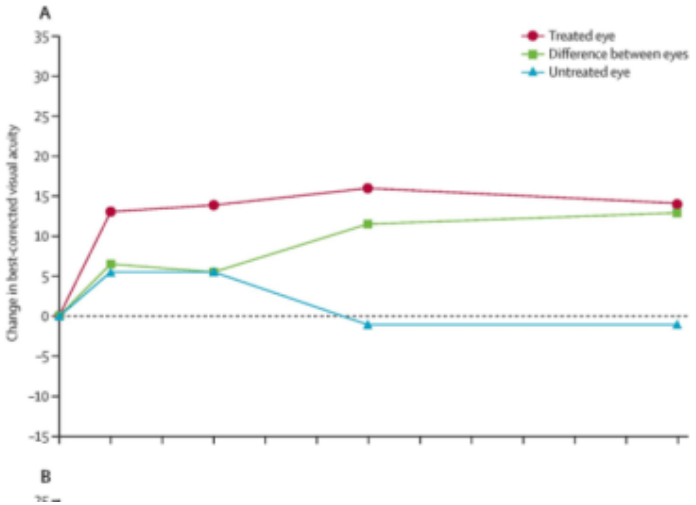
Special Issue

Subretinal Transplantation of Embryonic Stem Cell–Derived Retinal Pigment Epithelium for the Treatment of Macular Degeneration: An Assessment at 4 Years

Steven D. Schwartz,[1] Gavin Tan,[1,2] Hamid Hosseini,[1] and Aaron Nagiel[1]

[1]Retina Division, Stein Eye Institute, University of California Los Angeles Geffen School of Medicine, Los Angeles, California, United States
[2]Singapore Eye Research Institute, Singapore National Eye Centre, Singapore





VA improvement in the treated eye

DISADVANTAGES OF SUBRETINAL IMPLANTATION

- Uncontrolled bleb extension
- Cell reflux out of the bleb through the retinotomy and into the vitreous cavity.
- Reflux of cells may result in significant loss of efficacy and potentially side effects of cells being in the vitreous, for example, development of epiretinal membranes or retinal traction.
- The migratory potential of transplanted cells is not well appreciated.

PHASE 1 STUDY OF OUR GROUP

Oner et al. Stem Cell Research & Therapy (2016) 7:178
DOI 10.1186/s13287-016-0432-y

Stem Cell Research & Therapy

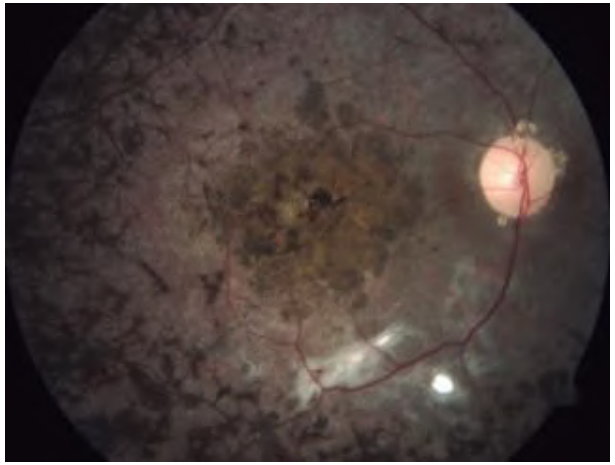
RESEARCH Open Access

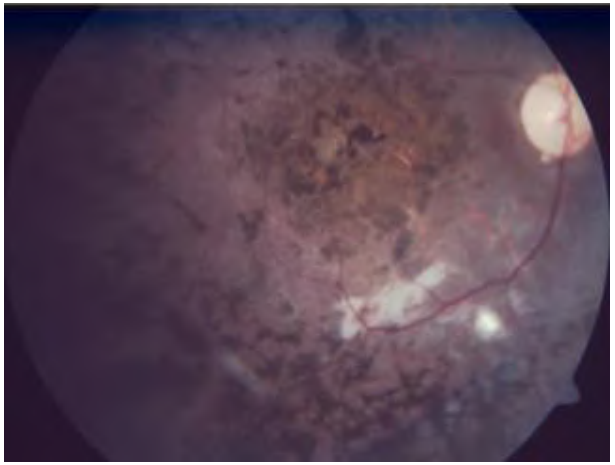
Subretinal adipose tissue-derived mesenchymal stem cell implantation in advanced stage retinitis pigmentosa: a phase I clinical safety study

Ayse Oner[1*], Z. Burcin Gonen[2,3], Neslihan Sinim[1], Mustafa Cetin[2,4] and Yusuf Ozkul[2,5]

Subretinal ADMSC implantation in 14 advanced RP patients

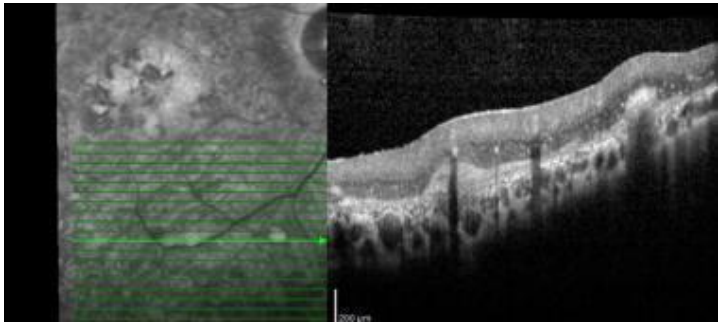
Subretinal Stem Cell Injection via 41 subretinal cannula (From our study)

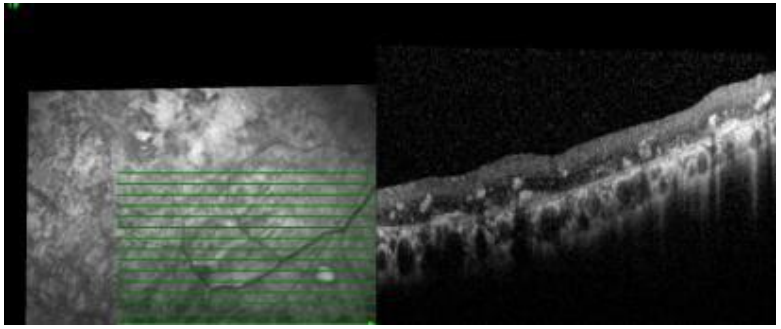


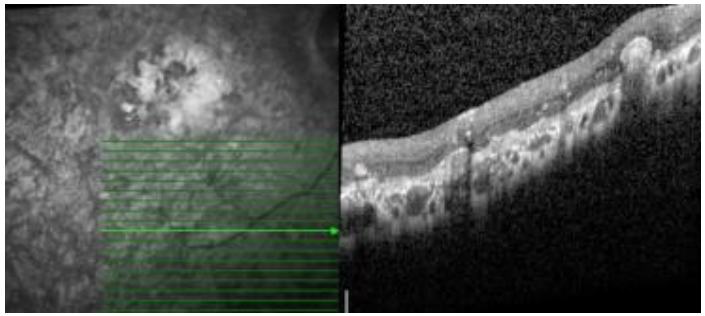


6. Month

4 years



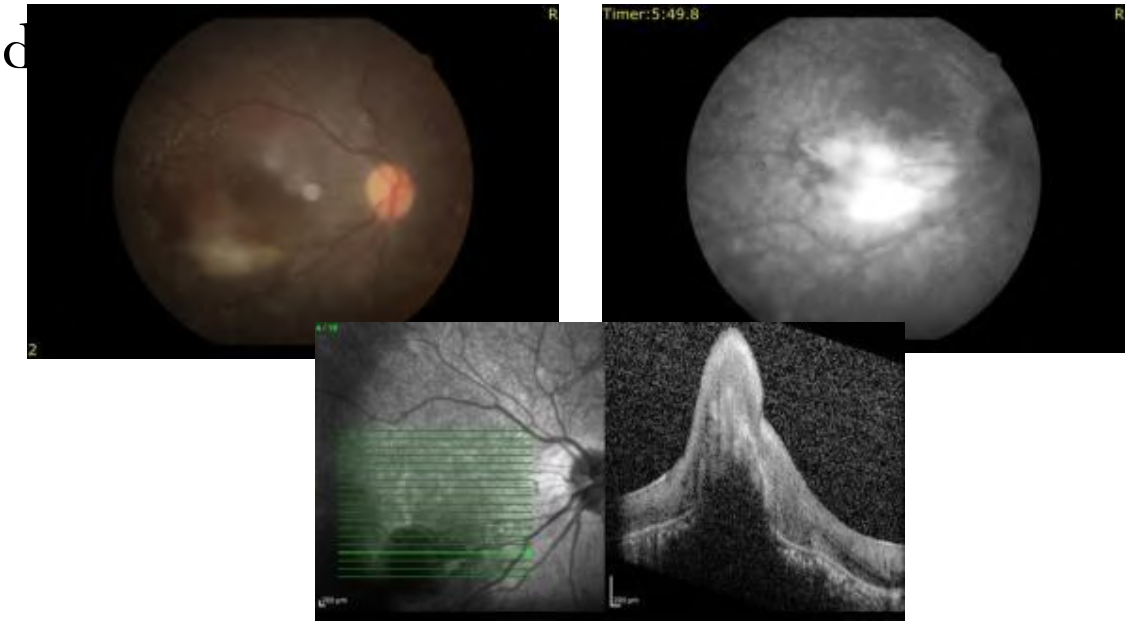




OCT scans of injection area, 1 month, 1 year, 4 years

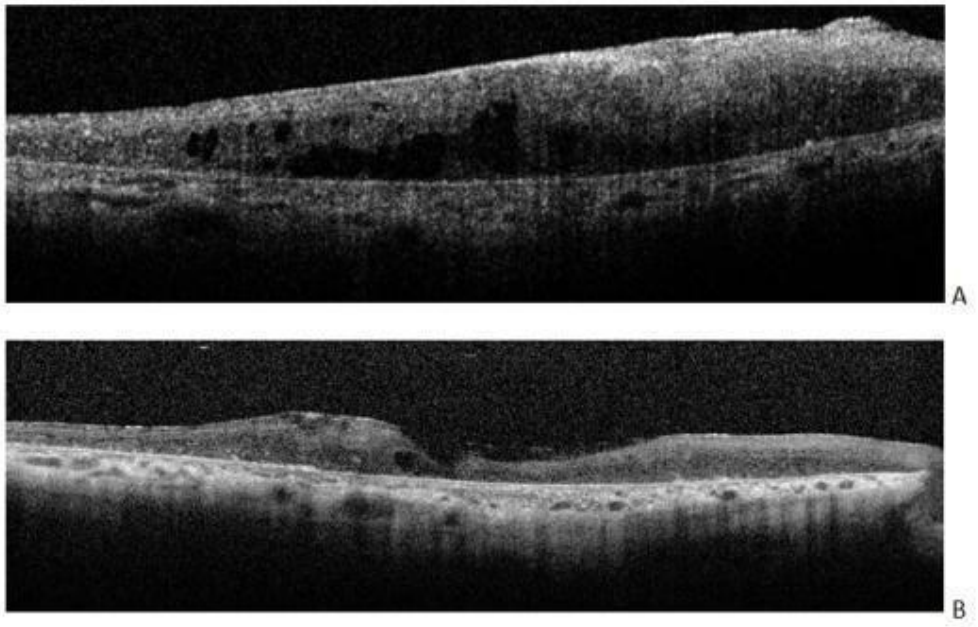
RESULTS OF OUR STUDY

- None of the patients had systemic complications.
- Eight patients had no ocular complications.
- One of the patients experienced choroidal neovascular membrane (CNM) and received intravitreal anti-VEGF d



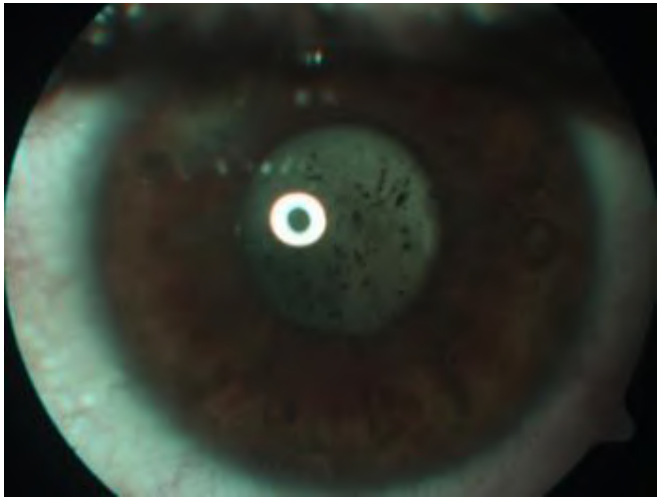
IMAGINGS OF THE PATIENT WITH CNVM

- The first operated six patients had epiretinal membrane (ERM) with localized peripheral tractional retinal detachment at the periphery which required second vitrectomy.



OCT OF A PATIENT WITH ERM AND OCT AFTER SECOND SURGERY

- Mild band keratopathy developed in one of these patients after six months and retrolental fibrous tissue was found in another patient after 12 months.



RETROLENTAL FIBROUS TISSUE

- Development of these membranes and fibrous tissue is thought to be due to the vitreal reflux or inadvertent preretinal injection and unwanted preretinal proliferation of MSCs.

- To prevent the occurance of this complication, the operation technique was modified (multiple air-fluid exchange to clear the MSC). This modification inhibited membrane formation in the remaining eight patients.

- Four patients experienced visual acuity improvement during the first year.

- The patients with visual acuity improvement were young with a relatively short duration of disease.

SUBRETINAL RPE SHEET INJECTION

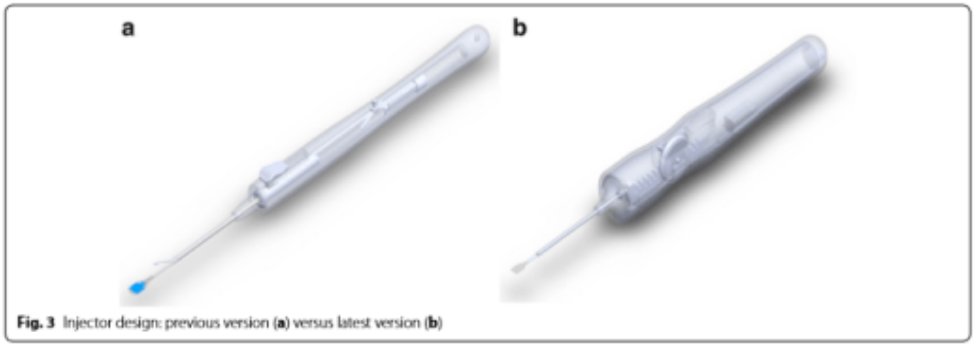


Fig. 3 Injector design: previous version (**a**) versus latest version (**b**)

THE INJECTOR

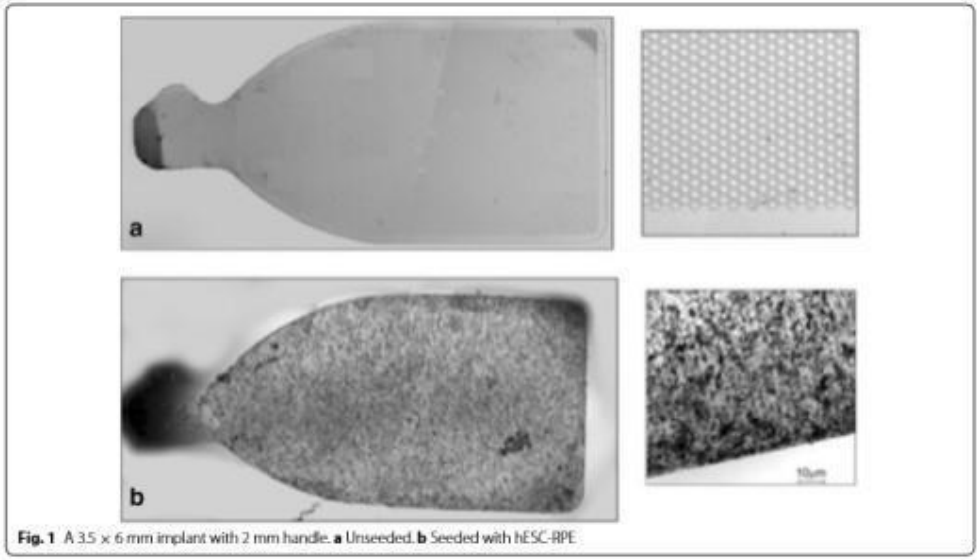


Fig. 1 A 3.5 × 6 mm implant with 2 mm handle. **a** Unseeded. **b** Seeded with hESC-RPE

RPE SHEET

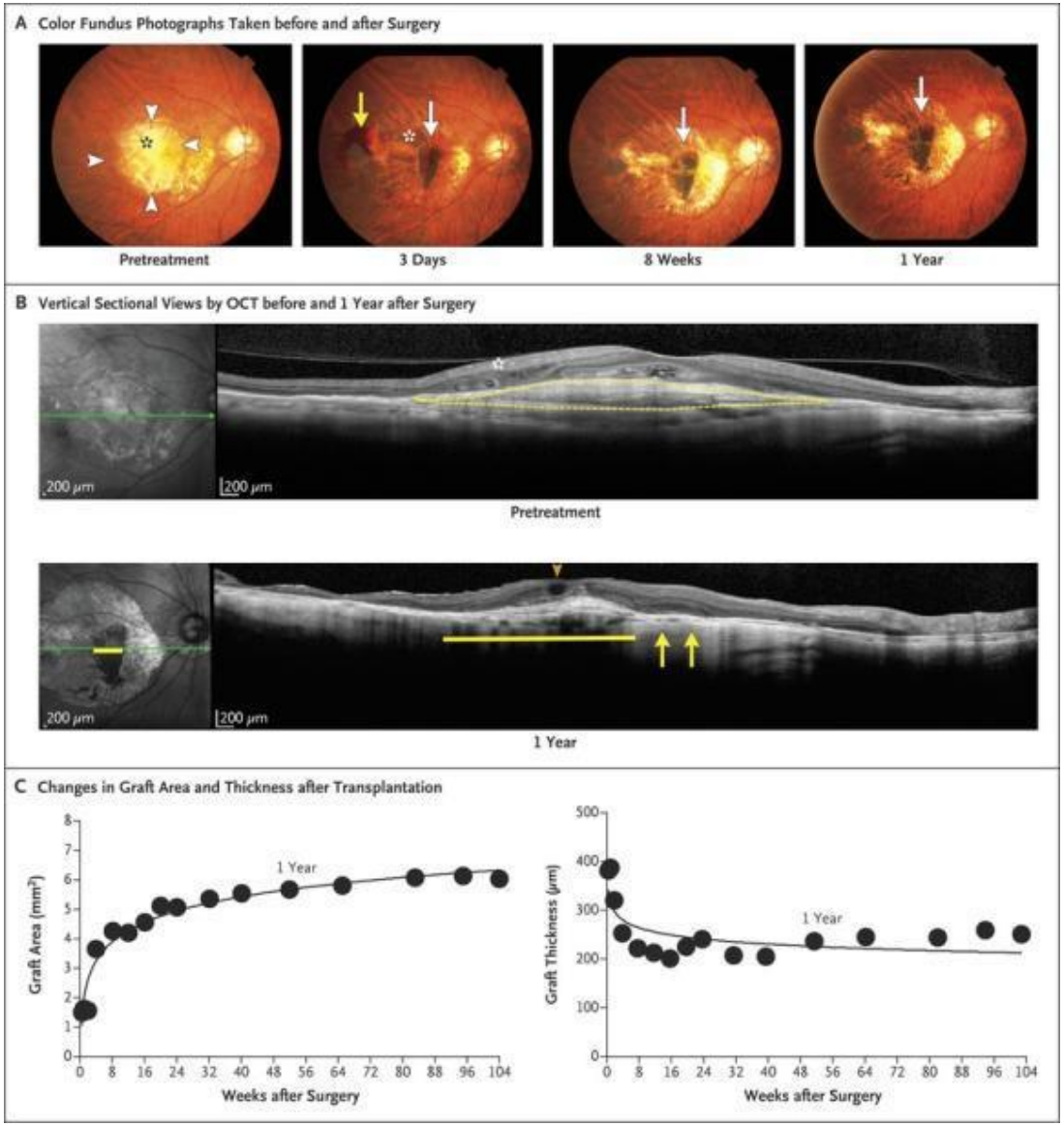
Fernandes et al. Int J Retin Vitr (2017) 3:41
DOI 10.1186/s40942-017-0095-6

International Journal of Retina and Vitreous

ORIGINAL ARTICLE Open Access

Development of a new tissue injector for subretinal transplantation of human embryonic stem cell derived retinal pigmented epithelium

Rodrigo A. Brant Fernandes[1,2†], Francisco R. Stefanini[1,2*†], Paulo Falabella[1,2], Michael J. Koss[1,3], Trent Wells[1], Bruno Diniz[1,2], Ramiro Ribeiro[1,2], Paulo Schor[2], Mauricio Maia[2], Fernando M. Penha[2,4], David R. Hinton[1,6], Yu-Chong Tai[5] and Mark Humayun[1,7]



A PATIENT WHO RECEIVED SUBRETINAL RPE SHEET

3- SUPRACHOROIDAL

- 1: Suprachoroidal cannulation via silicone catheters (MicroTrac catheter; i Science Interventional, Menlo Park, CA)

- 2: Limoli Technique (You will listen from the master)

- Safer than vitrectomy plus subretinal injection
- There is no removal of the vitreous and no iatrogenic retinal hole.

LIMOLI TECHNIQUE

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 30

Research Paper: Gerotarget (Focus on Aging)

Cell surgery and growth factors in dry age-related macular degeneration: visual prognosis and morphological study

Paolo Giuseppe Limoli[1], Celeste Limoli[1], Enzo Maria Vingolo[2], Sergio Zaccaria Scalinci[3] and Marcella Nebbioso[4]

J Vis Exp. 2018 Feb 12;(132). doi: 10.3791/56469.

Regenerative Therapy by Suprachoroidal Cell Autograft in Dry Age-related Macular Degeneration: Preliminary In Vivo Report.

Limoli PG[1], Vingolo EM[2], Limoli C[1], Scalinci SZ[3], Nebbioso M[4].

Table 3: Patient compliance analysis (PCA) shows that, at 6 months post surgery, 19 of 36 eyes (52.78%) recorded better vision, 14 (38.89%) no change in functional situation, and 3 (8.33%) a worsening.

PCA	Group A	Group B	Total
Number of eyes	14	22	36
Improved (%)	5 (35.71)	14 (63.64)	19 (52.78)
Unchanged (%)	7 (50)	7 (31.82)	14 (38.89)
Worse (%)	2 (14.29)	1 (4.55)	3 (8.33)

Among the 19 eyes of patients who noted an improvement at 6 months post surgery, 5 (26.3%) belong to group A and 14 (73.7%) to group B.

CELLULAR REPROGRAMMING
Volume 20, Number 6, 2018

DOI: 10.1089/cell.2018.0045

Brief Communication

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

Ayse Oner,[1] Zeynep Burcin Gonen,[2,3] Duygu Gülmez Sevim,[4]
Neslihan Smim Kahraman,[4] and Metin Unlu, MD[5]

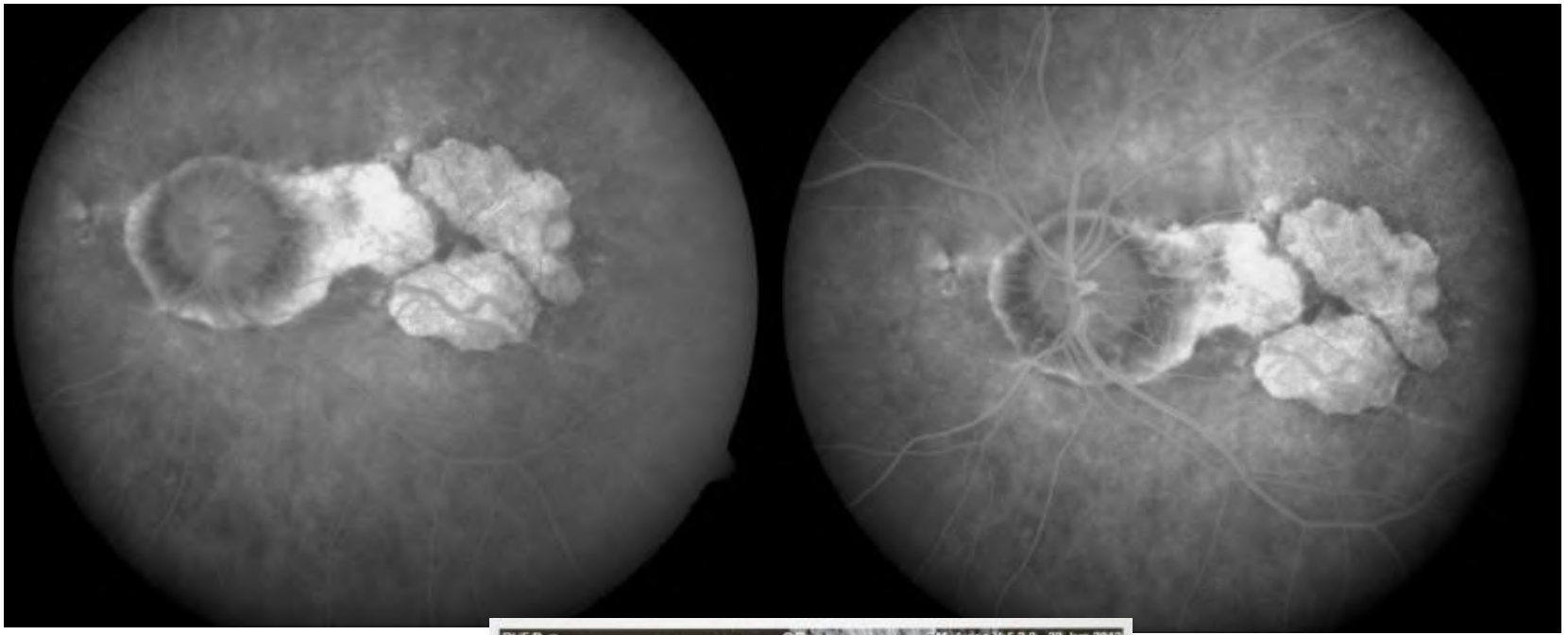
Int Ophthalmol
https://doi.org/10.1007/s10792-019-01141-5

ORIGINAL PAPER

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

Ayse Oner · Zeynep Burcin Gonen · Duygu Gülmez Sevim · Neslihan Sinim Kahraman · Metin Unlu

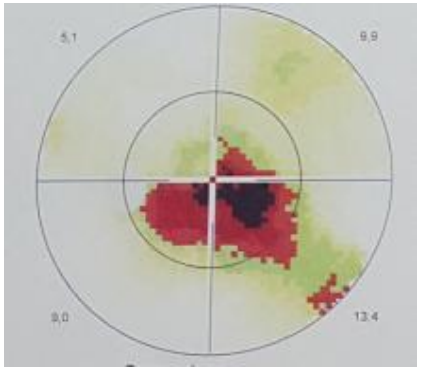
PUBLICATIONS OF OUR GROUP



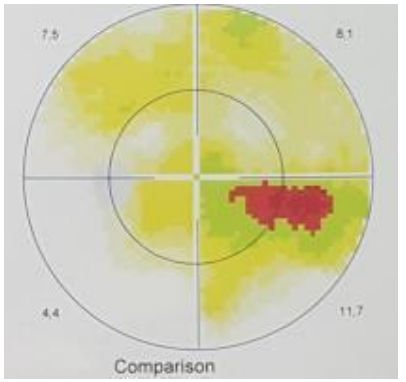
USG of the fleb area

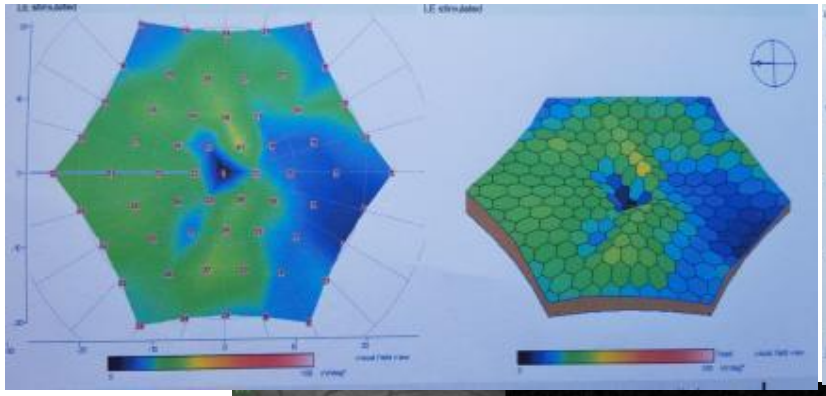
BEFORE

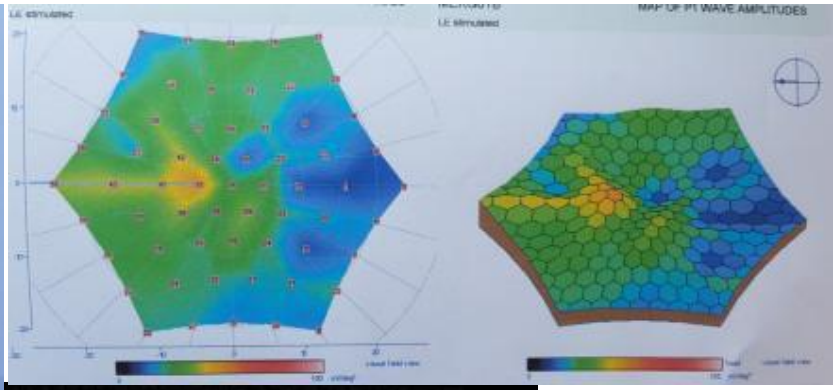
AFTER

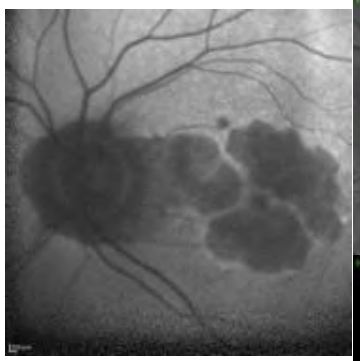


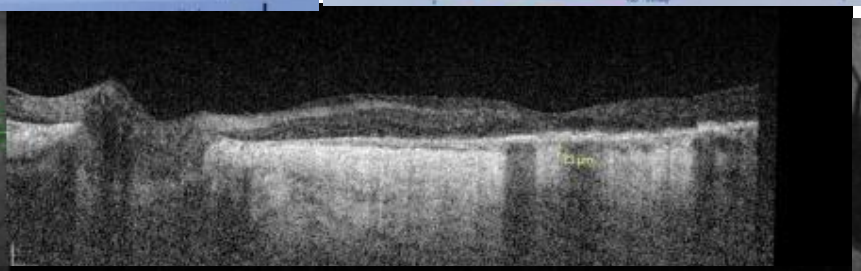
65 yrs old male, AMD
VA: From 1 mcf to 0.05
VISUAL FIELD, ERG, OCT

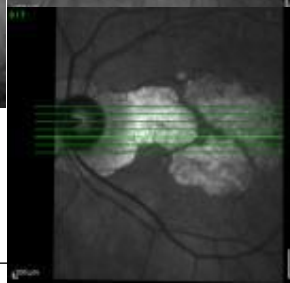


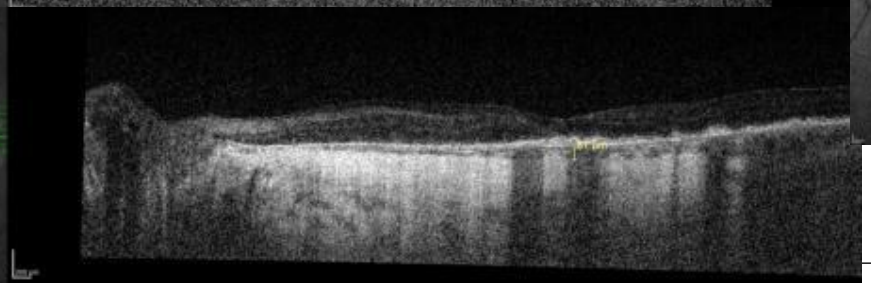


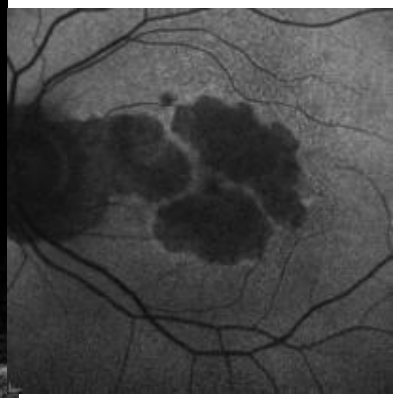






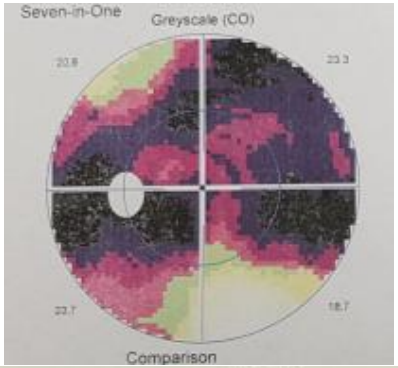






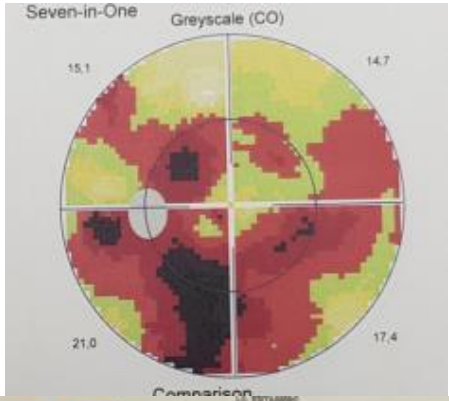
BEFORE

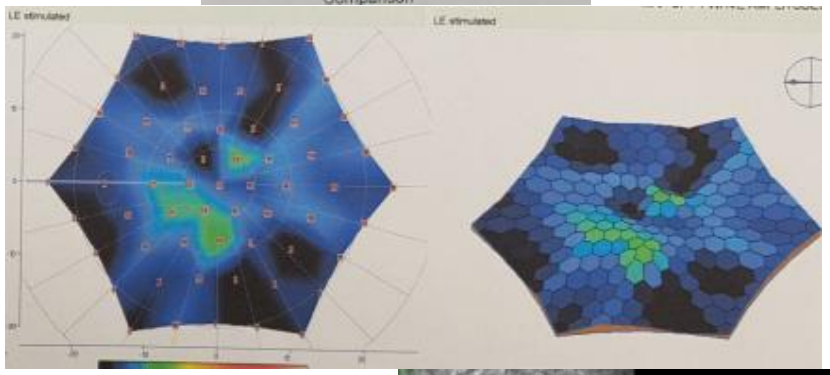
AFTER

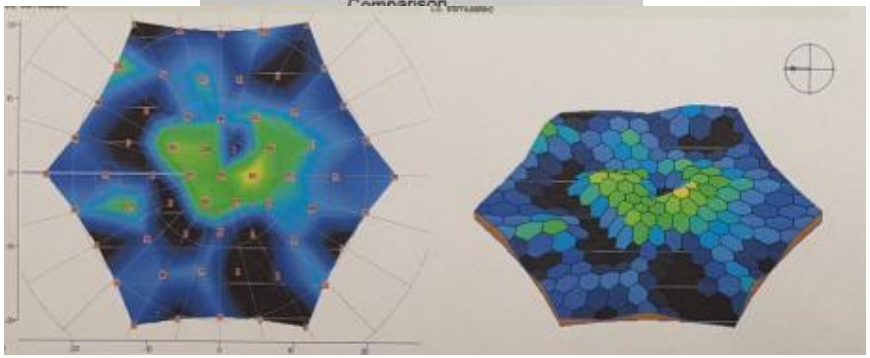


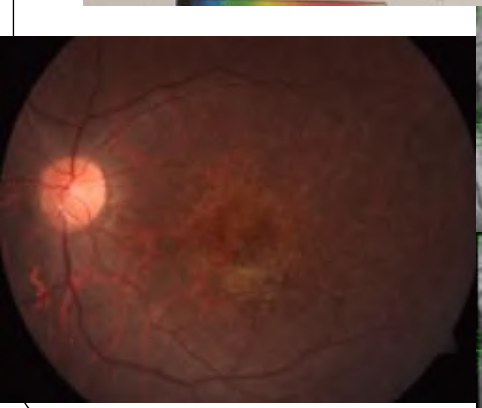
27 yrs old female
VA: From1 mcf to 0.05

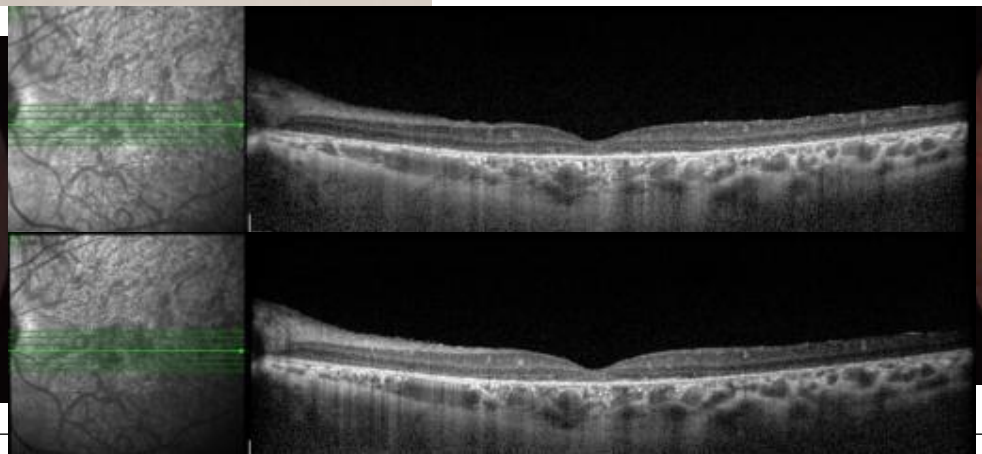
VISUAL FIELD, ERG,OCT

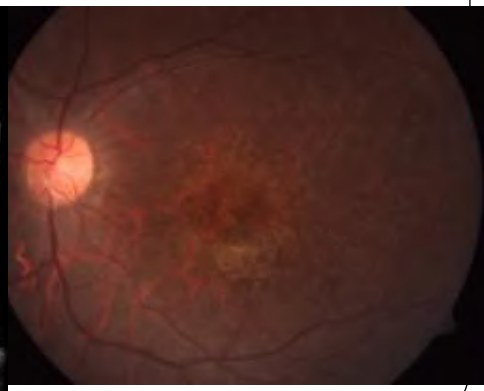




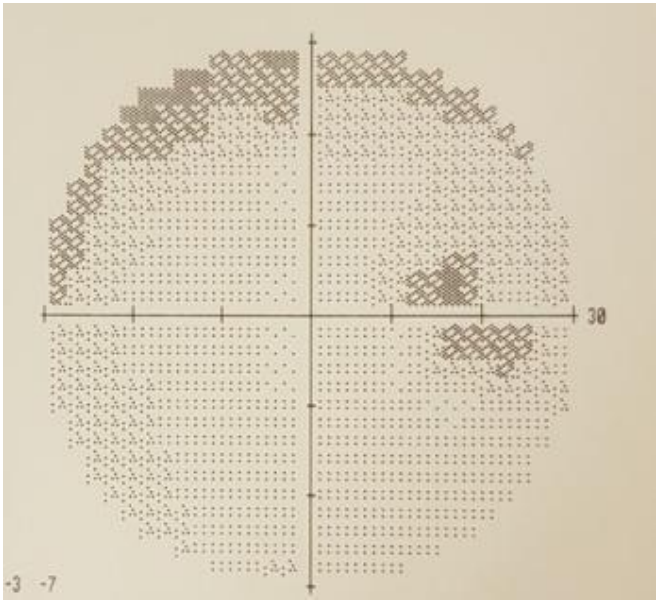








56 yrs old male, AMD



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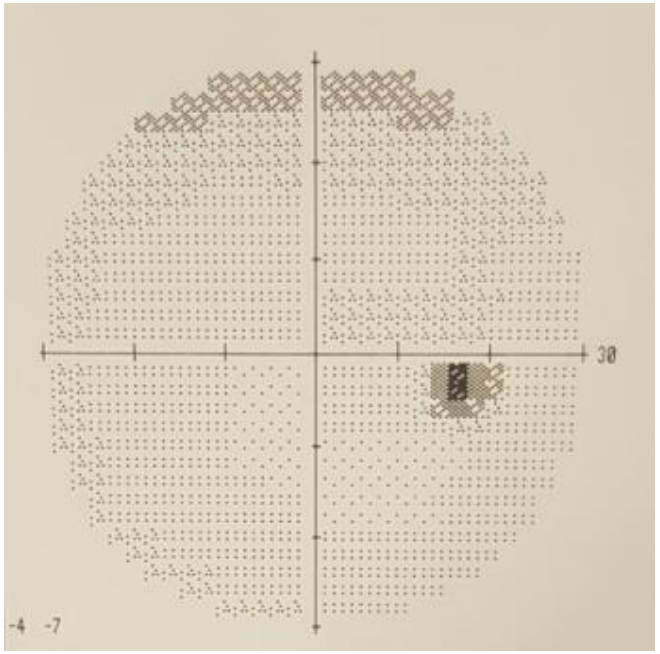
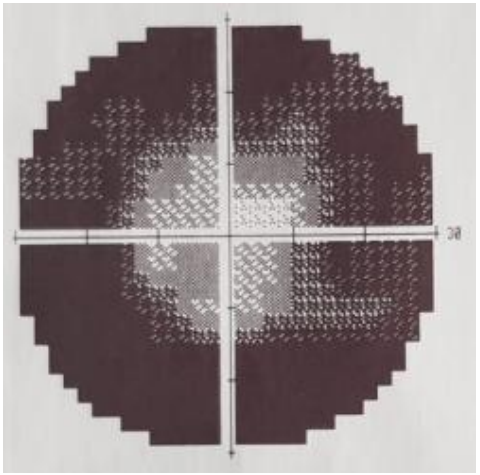


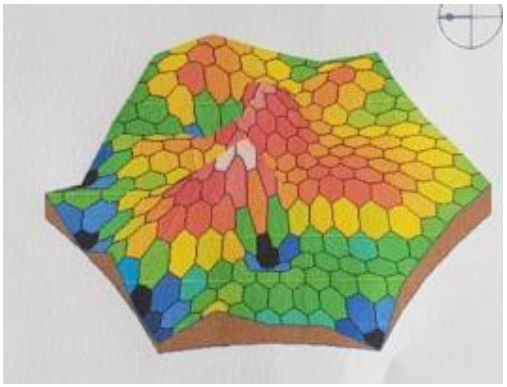
AFTER

VA: From 0.4 to 0.7.

48 yrs old female RP. GA: From 0.4 to 0.6

BEFORE





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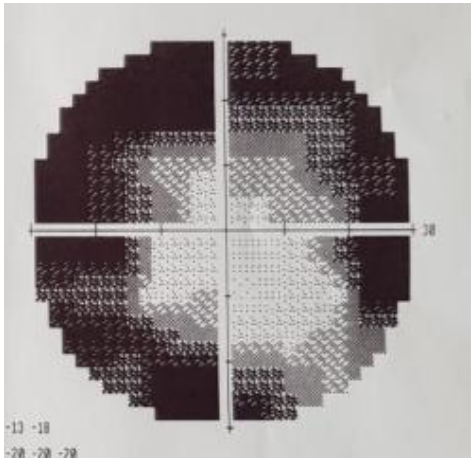

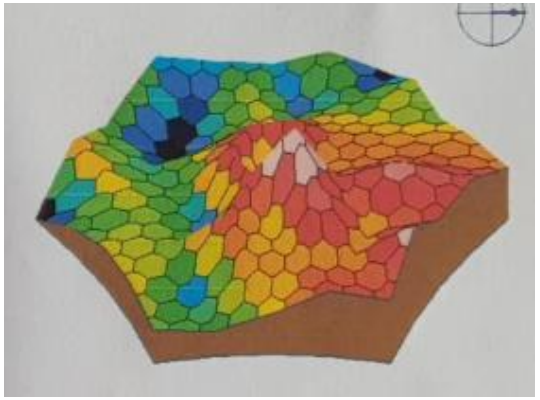

4,5- Subtenon, Intravenous

- SCOTS: Stem Cell Ophthalmology Treatment Study

- 3 Arms in SCOTS

  1- Intravitreal+ Intravenous

  2- Subtenon/Retrobulbar+Intravenous

  3- Subretinal/Intra optic nerve+Intravenous

Original Article

Stem Cell INVESTIGATION

Stem Cell Ophthalmology Treatment Study: bone marrow derived stem cells in the treatment of non-arteritic ischemic optic neuropathy (NAION)

Jeffrey N. Weiss[1], Steven Levy[2], Susan C. Benes[3]

Background: Ten patients with bilateral visual loss due to sequential non-arteritic ischemic optic neuropathy (NAION) underwent autologous Bone Marrow Derived Stem Cell (BMSC) therapy within the Stem Cell Ophthalmology Treatment Study (SCOTS). SCOTS is an Institutional Review Board approved clinical study utilizing autologous BMSC in the treatment of optic nerve and retinal diseases that meet inclusion criteria.

Methods: The average age of the patients treated was 69.8 years. The average duration of visual loss in eyes treated was 9.8 years and ranged from 1 to 35 years. Affected eyes were treated with either retrobulbar, subtenons and intravenous BMSC or, following vitrectomy, intra-optic nerve, subtenons and intravenous BMSC. The primary outcome was visual acuity as measured by Snellen or converted to LogMAR.

Results: Following therapy in SCOTS, 80% of patients experienced improvement in Snellen binocular vision (P=0.029) with 20% remaining stable; 73.6% of eyes treated gained vision (P=0.019) and 15.9% remained stable in the post-operative period. There was an average of 3.53 Snellen lines of vision improvement per eye with an average 22.74% and maximum 83.3% improvement in LogMAR acuity per eye. The average LogMAR change in treated eyes was a gain of 0.364 (P=0.0089). Improvements typically manifested no later than 6 months post procedure.

Original Article

Stem Cell INVESTIGATION

Stem Cell Ophthalmology Treatment Study: bone marrow derived stem cells in the treatment of Retinitis Pigmentosa

Jeffrey N. Weiss[1], Steven Levy[2]

2018-Haziran

Results: Following therapy in SCOTS or SCOTS 2, 11 patients (64.7%) showed improved binocular vision averaging 10.23 lines of Snellen acuity per eye over pre-treatment acuity; 8 patients (35.3%) remaining stable over the follow up period; no patients experiencing loss of overall acuity. In 33 treated eyes, 15 eyes (45.5%) improved an average of 7.9 lines of Snellen acuity, 15 eyes (45.5%) remained stable, and 3 eyes (9%) worsened by an average of 1.7 lines of Snellen acuity. Improvements ranged from 1 to 27 lines of vision. Using the LogMAR Scale and calculating delta as a ratio to pre-treatment vision in improved eyes, acuity improvement ranged from 23% to 90% with an average of 40.9% visual acuity improvement over baseline vision. Evaluation of all patients and eyes capable of LogMAR vision showed an average of 31% improvement in vision over baseline. Findings were of statistical significance (P=0.016). There were no surgical complications.

CONCLUSIONS:

- The results of the first clinical studies provide evidence of beneficial effects of stem cell implantations in degenerative retinal and optic nerve diseases.

- To optimize the cell delivery technique and to evaluate the effects of SC therapy on visual acuity and the quality of life of these patients, future studies with larger number of cases will be necessary.