İleri evre retinitis pigmentozalı iki olgunun subretinal mezenkimal kök hücre implantasyonu sonrasında 4 yıllık takip sonuçları

Prof. Dr. Ayşe Öner, FEBO
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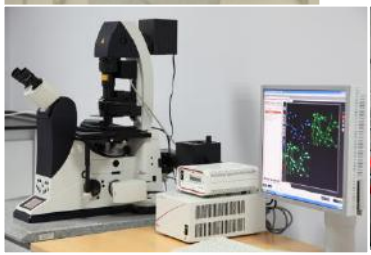
ERCİYES ÜNİVERSİTESİ TIP FAKÜLTESİ
GÖZ HAST VE GENKÖK /KAYSERİ

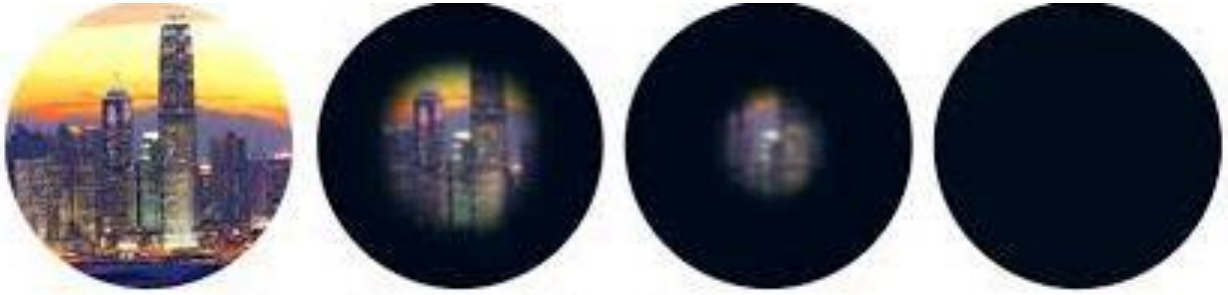


RETİNİTİS PİGMENTOSA
TAVUK KARASI-GECE KÖRLÜĞÜ

- Öncelikle gece görmeyi sağlayan rod hücrelerini
- Daha sonrada gündüz görmeyi sağlayan kon hücrelerini ve RPE'yi etkileyen
- İlerleyici, dejeneratif, genetik geçişli bir retina hastalığıdır.
- Görülme sıklığı farklı çalışmalarda 1/3000-4000 olarak bildirilmektedir.
- Farklı kalıtsal geçişlerle kendini gösterebilir.
- Günümüzde bilinen etkin bir tedavisi henüz yoktur.

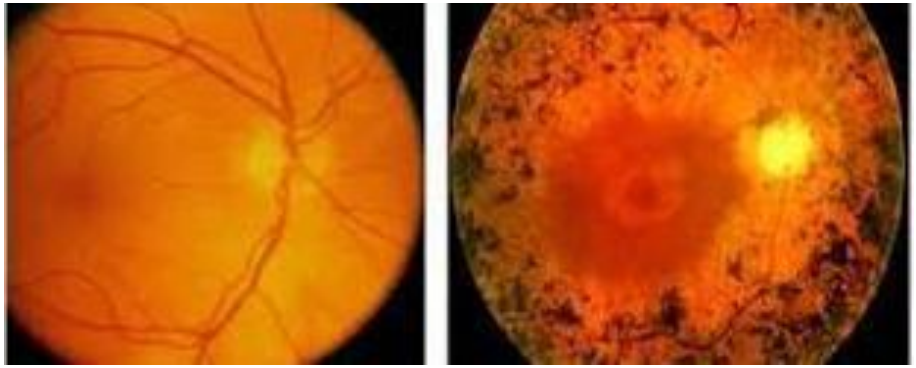
SEYİR

- Başlangıç yaşı erken çocukluktan erişkin olarak daha ileri yaşlara kadar değişir.
- RP gece körlüğü, görme alanında ilerleyen daralma, tünel içinden görüş ve son aşamada da total körlükle sonuçlanır.

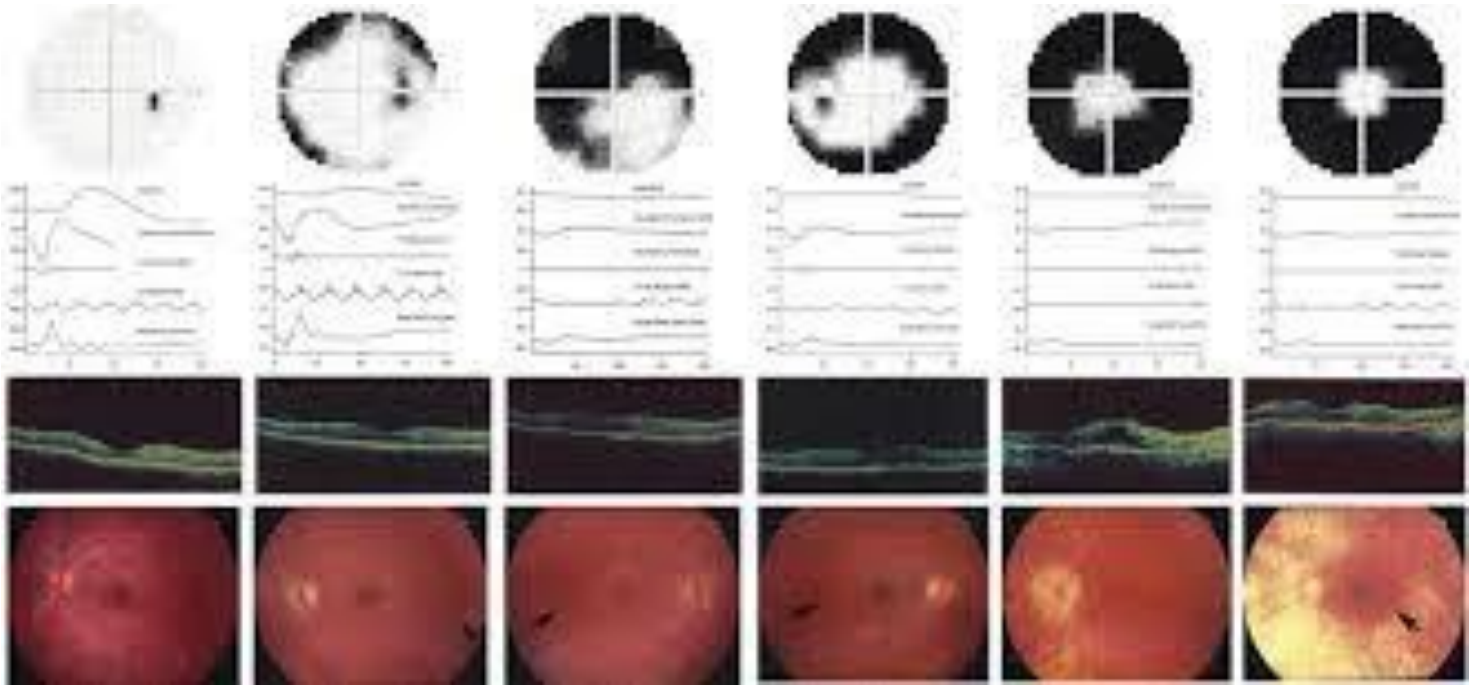


BULGULAR

- Soluk optik disk
- Dar retina damarları
- Retinadaki pigment değişiklikleri,



BULGULAR



AMAÇ

- İleri evre retinitis pigmentozalı (RP) iki olgunun subretinal mezenkimal kök hücre (MKH) implantasyonu sonrasında 4 yıllık takip sonuçlarını sunmak amaçlanmıştır.
- **Faz I güvenilirlik çalışması**
- Tek doz, subretinal, adipoz doku derive allojenik MKH uygulaması

ONAY AŞAMALARI

- Etik Onay
- Sağlık Bakanlığı Doku ve Kök Hücre Nakli Birimi
- Proje Onayı

HASTALAR VE METOD

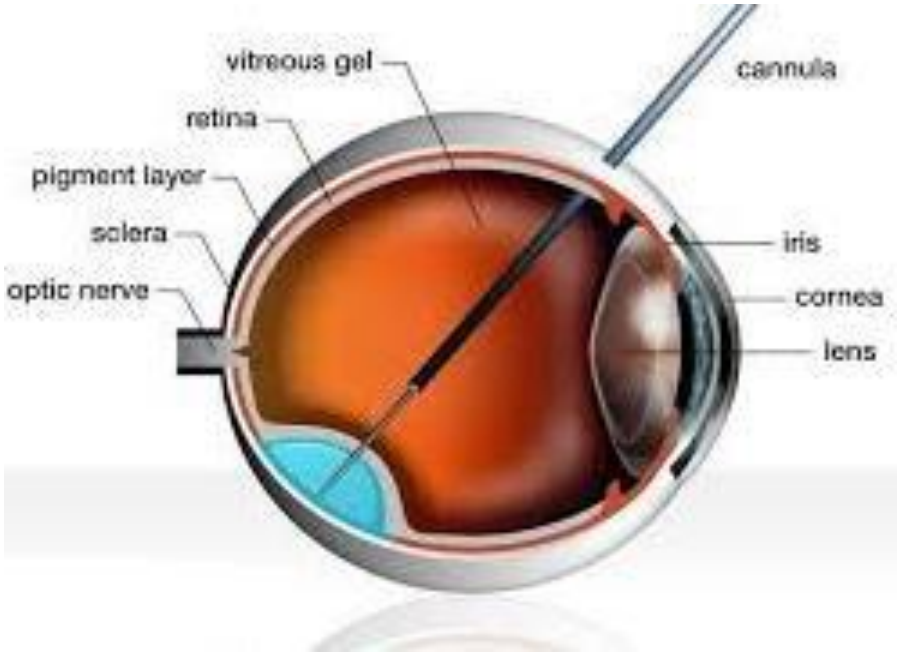
- Gönüllülerin araştırmaya dâhil edilme kriterleri:
- 1-Oftalmolojik olarak ve elektrofizyolojik olarak RP tanısının doğrulanmış olması.
- 2- 18 yaşının üzerinde olması
- 3-Görme düzeyinin 0.05 ve altında olması
- 4- Olgunun ek oftalmolojik ve sistemik probleminin olmaması

TESTLER

- Hastanın tek gözü (daha az gören gözü) çalışmaya alındı.
- Tedavi öncesinde yapılan testler rutin oftalmolojik testler
- Fundus floresein anjiografi (FFA)
- Optik kohorens tomografi (OKT)
- Periferik görme alanı testi (PGA)
- Elektroretinografi (ERG) testleri yapıldı.

UYGULAMA

- MKH'ler Erciyes Üniversitesi bünyesinde bulunan GENKÖK merkezinden elde edilmiş.
- Hücrelerin MKH olduğu; MKH belirteçleri ile doğrulanmıştır.
- Gönderilecek son ürününden kalite kontrol testleri yapıldıktan sonra hasta uygulaması için gönderilmiştir.
- 0.1 ml 'de tek doz 3.pasajda, $20X10^6$ adipoz doku kaynaklı MKH uygulaması yapılmıştır.
- 23 gauge ile total vitrektomi sonrası 2.milyon subretinal MKH enjekte edildi.


vitreous gel
retina
pigment layer
sclera
optic nerve
cannula
iris
cornea
lens

ADMKH ler uluslar arası GMP standartlarında üretildi

BULGULAR

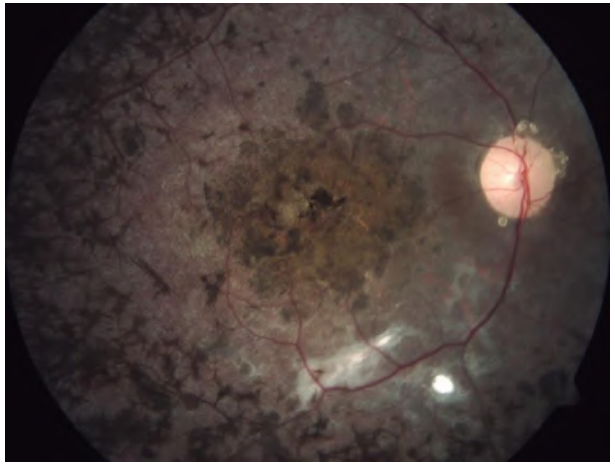
- 2 olgunun da 4 yıllık takipleri tamamlanmıştır.
- İki olguda da sistemik ve okuler komplikasyon görülmemiştir.
- İki olguda da FFA testlerinde patolojiye rastlanmamıştır.

SONUÇLAR

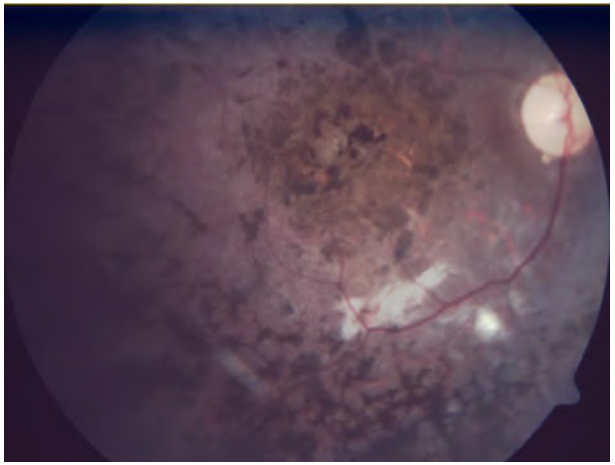
- 2 olguda belirgin görme artışı olmuş, bu artış 4. yılda da devam etmiştir.

- Görme artışı olan bu olgular preop görmesi iyi olan olgulardır.

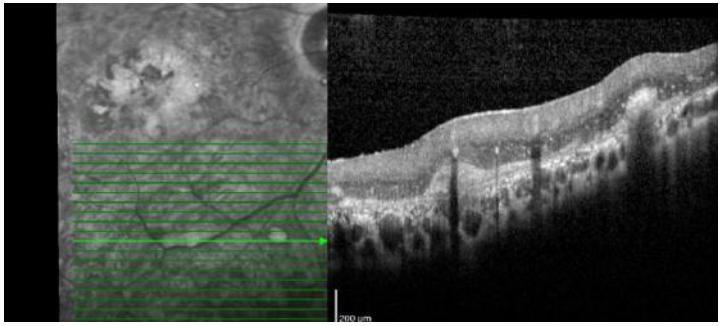
- Bir olguda EİDGK 0.01’den 0.05’e diğer olguda ise 1 mps den 2 mps düzeyine yükselmiştir.

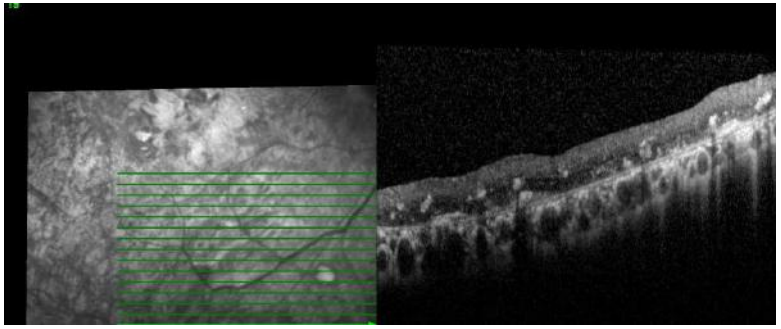


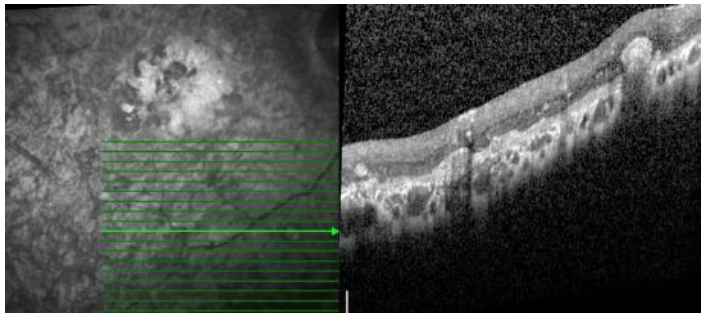
6. Ay fundus görüntüsü



4 yıl fundus görüntüsü

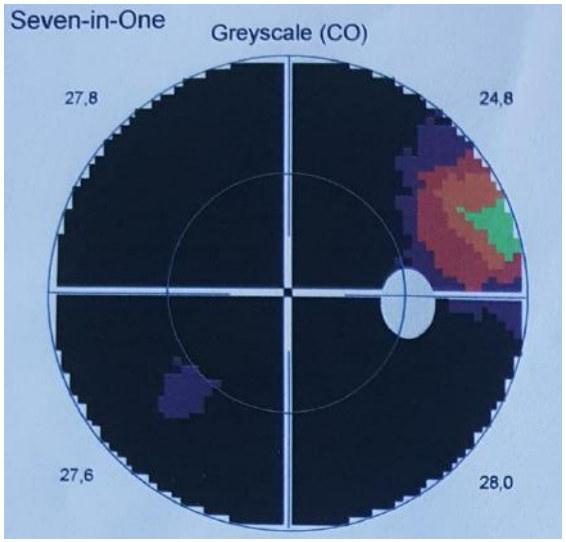


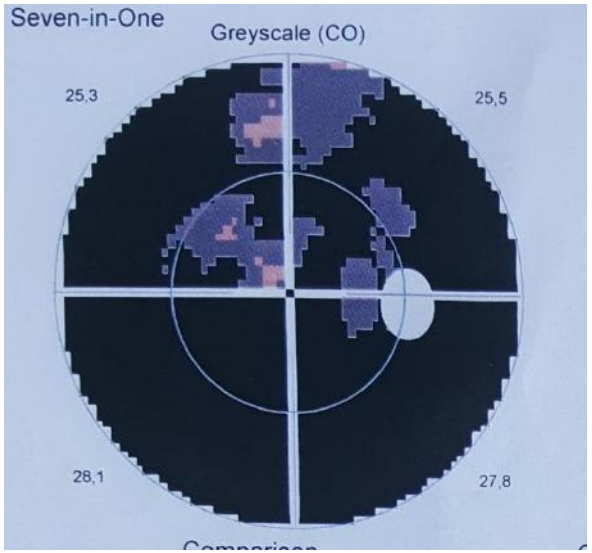


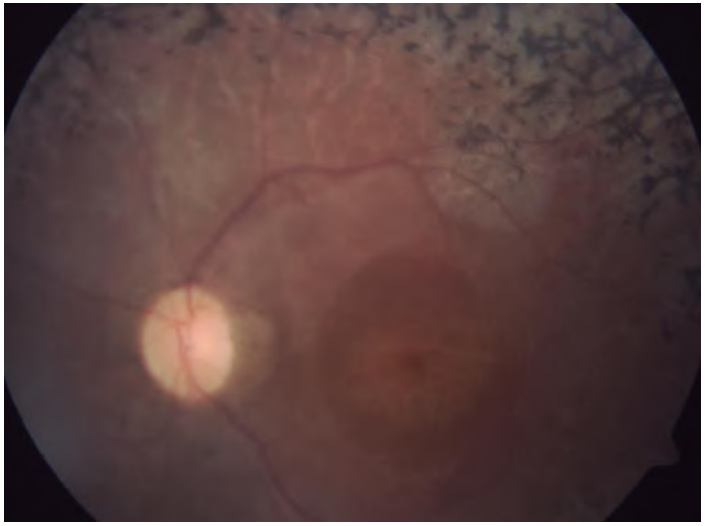


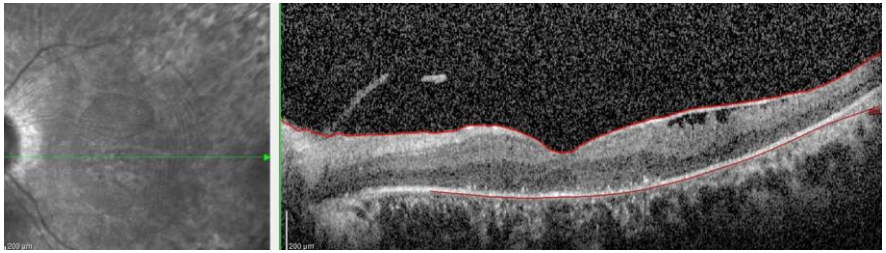
1 ay, 1. yıl ve 4. yılda enjeksiyon alanında OCT görünümü

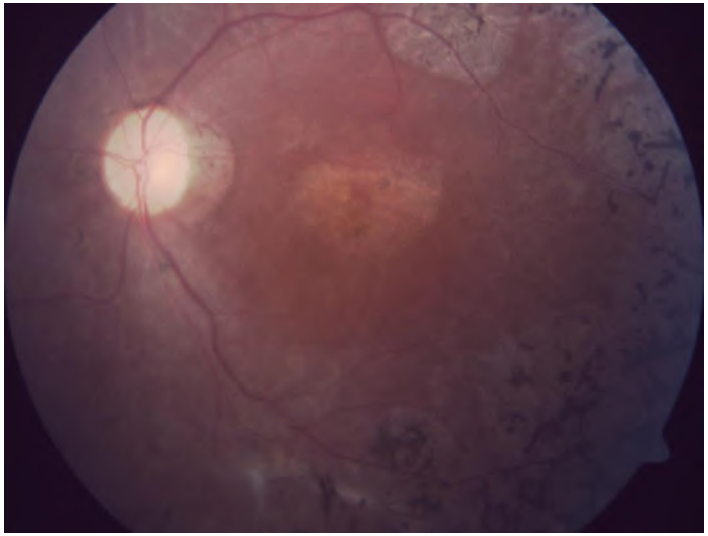

Greyscale (CO)
26,3
26,8
Comparison

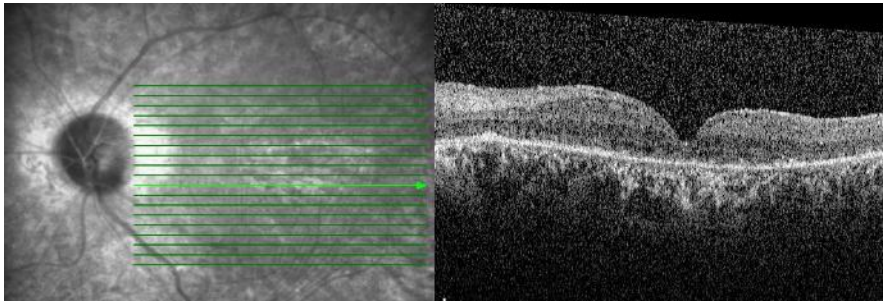

Seven-in-One
Greyscale (CO)
27,8
24,8
27,6
28,0

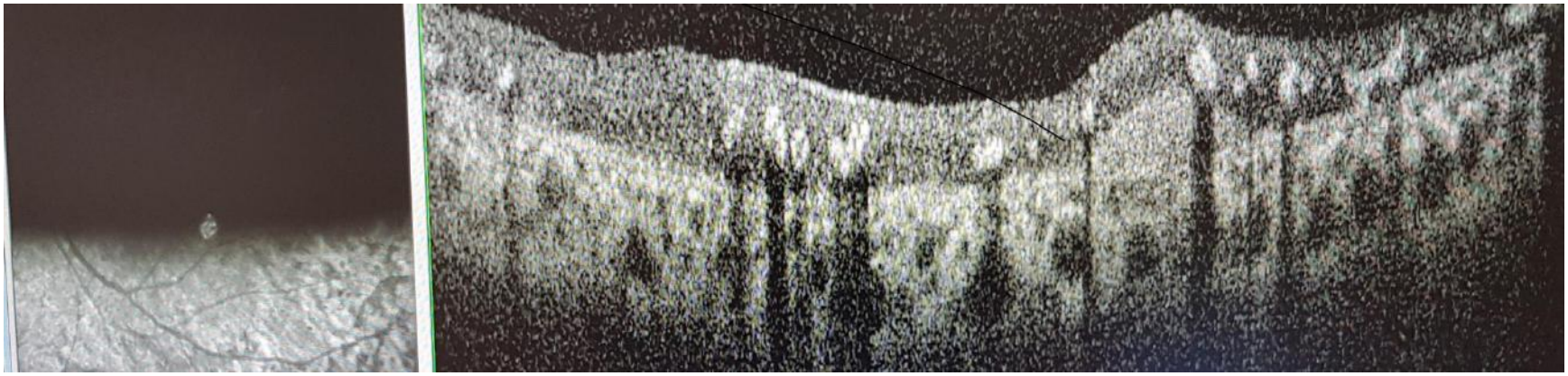

Seven-in-One
Greyscale (CO)
25,3
25,5
28,1
27,8

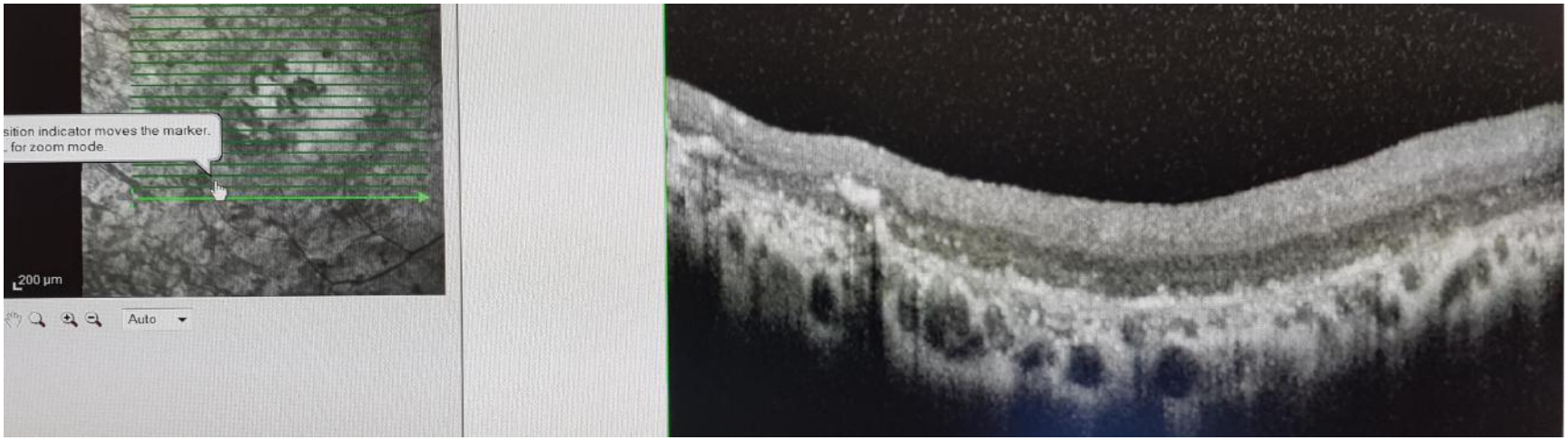


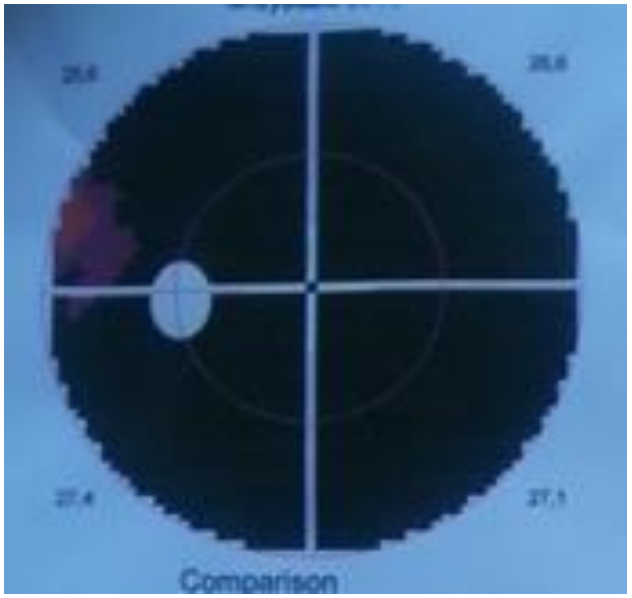


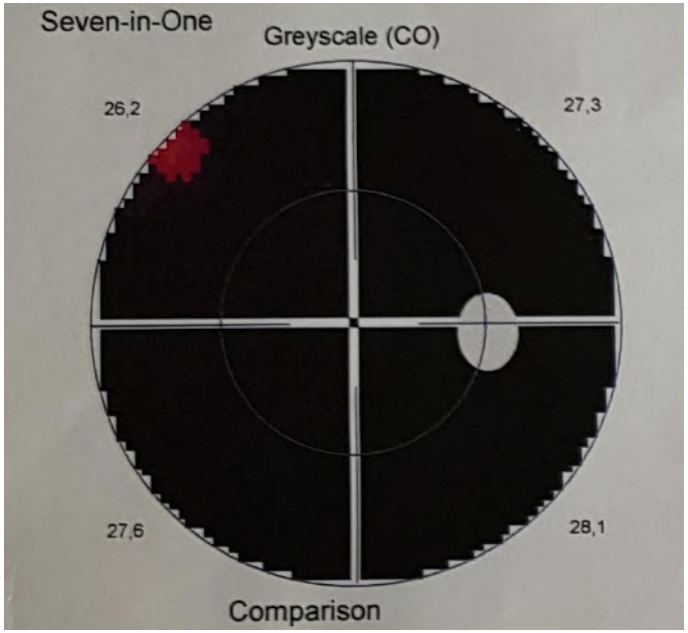


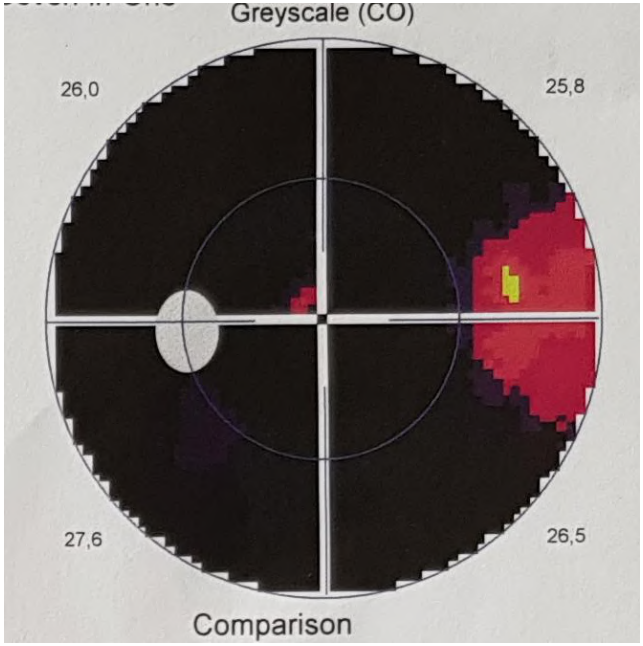


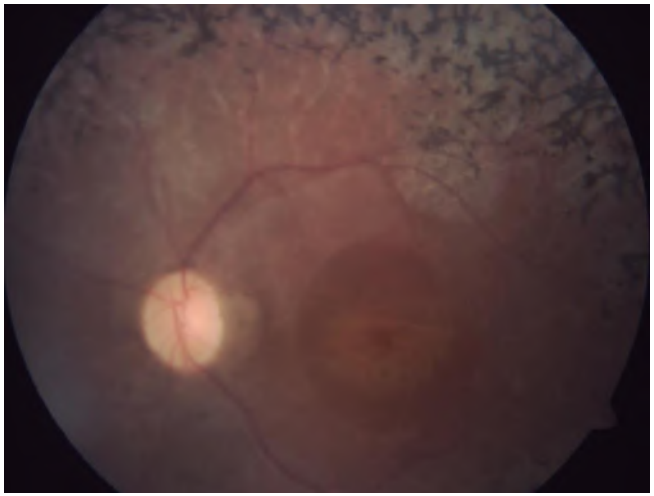


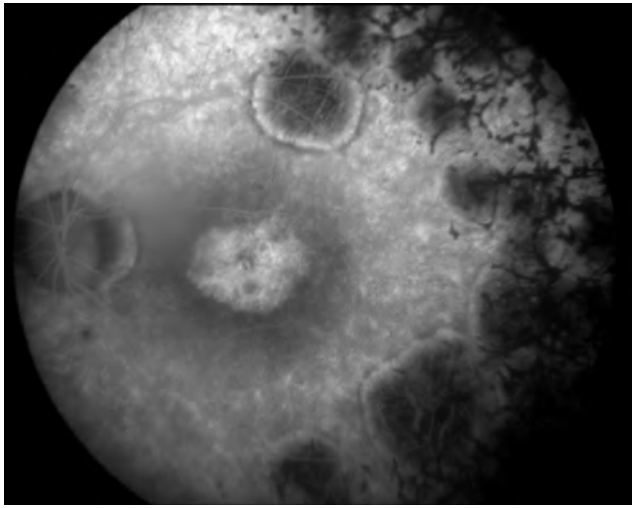

sition indicator moves the marker.
for zoom mode.
200 µm
Auto

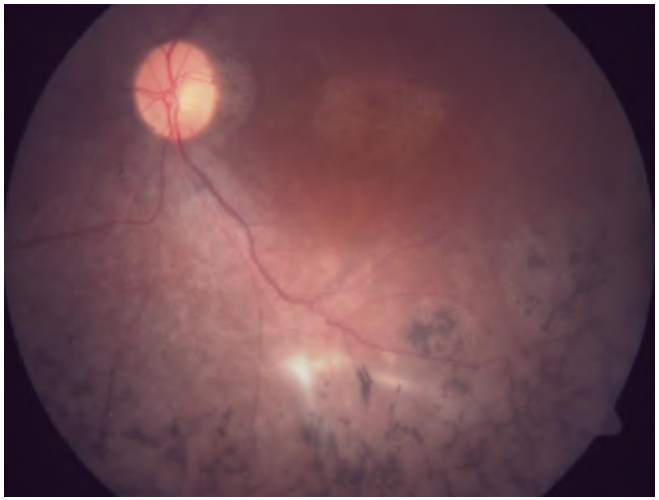

Comparison

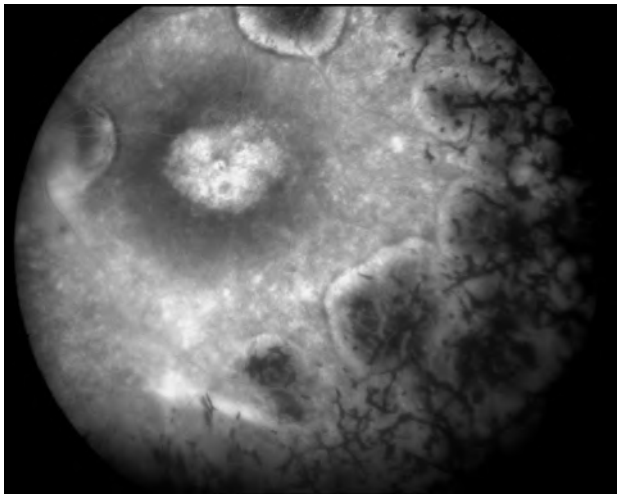

Seven-in-One
Greyscale (CO)
26,2
27,3
27,6
28,1
Comparison

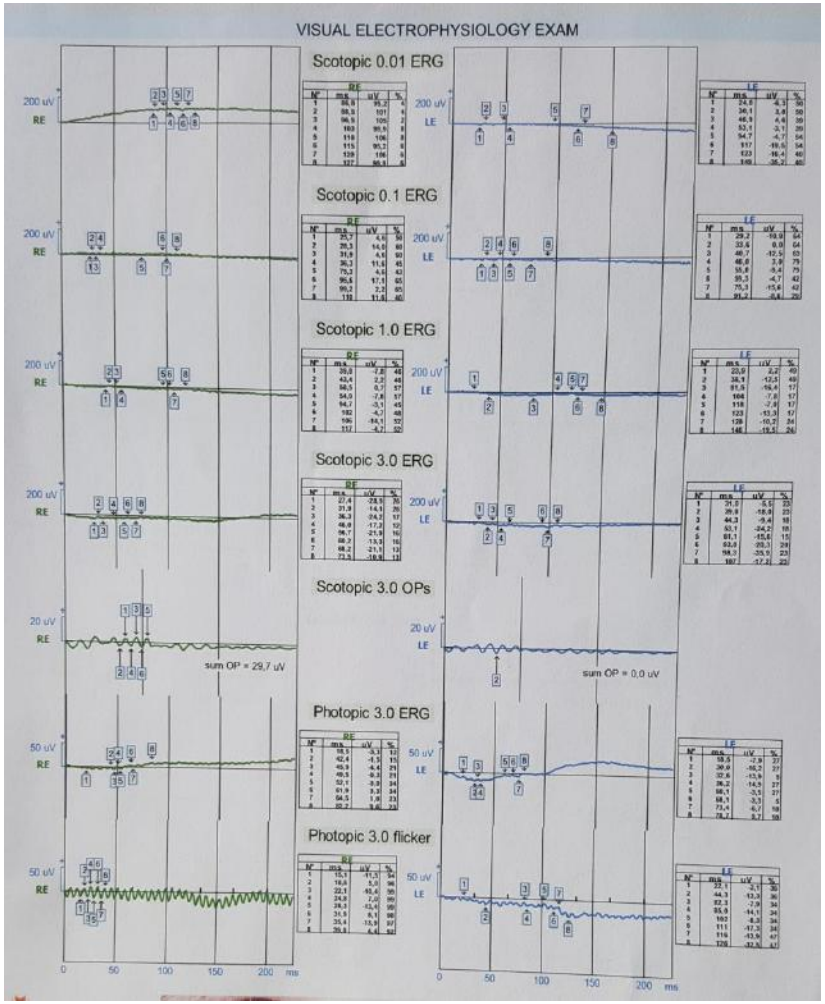

Greyscale (CO)
26,0
25,8
27,6
26,5
Comparison

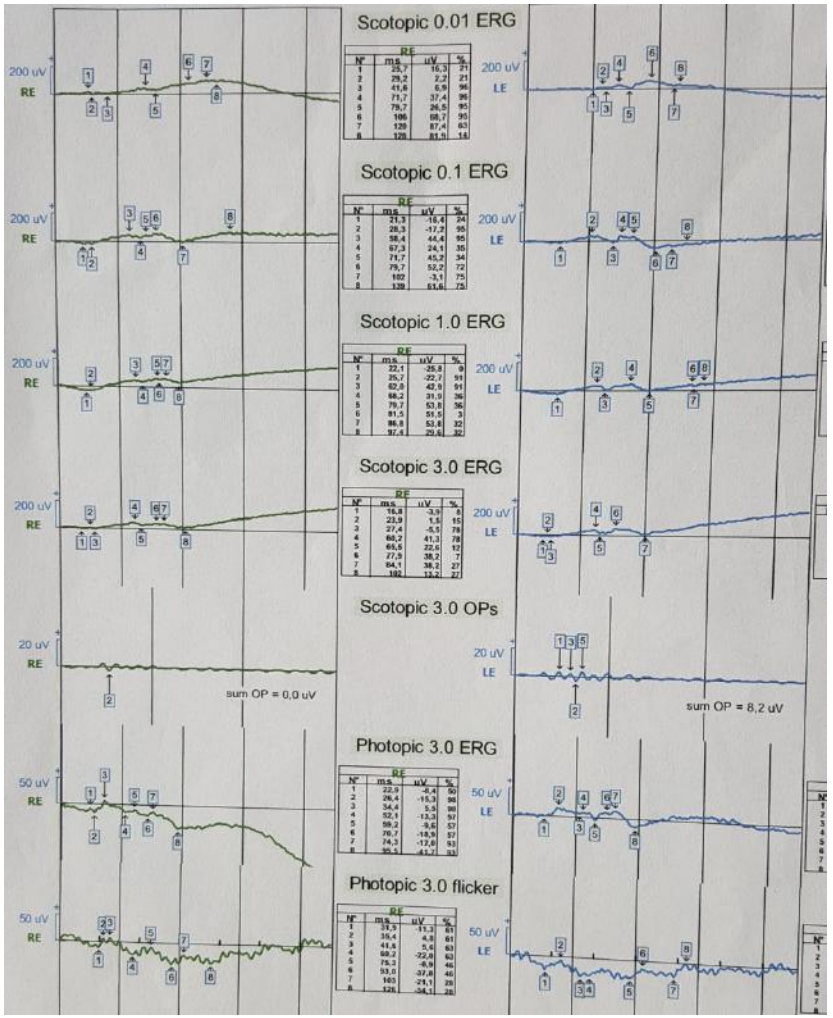









VISUAL ELECTROPHYSIOLOGY EXAM
Scotopic 0.01 ERG
Scotopic 0.1 ERG
Scotopic 1.0 ERG
Scotopic 3.0 ERG
Scotopic 3.0 OPs
sum OP = 29,7 uV
sum OP = 0,0 uV
Photopic 3.0 ERG
Photopic 3.0 flicker
RE
LE
200 uV
20 uV
50 uV
0
50
100
150
200
ms


Scotopic 0.01 ERG
Scotopic 0.1 ERG
Scotopic 1.0 ERG
Scotopic 3.0 ERG
Scotopic 3.0 OPs
sum OP = 0,0 uV
sum OP = 8,2 uV
Photopic 3.0 ERG
Photopic 3.0 flicker
RE
LE
200 uV
20 uV
50 uV

RP'DA MKH İLK ÇALIŞMA-RETİCELL

- Prospektif bir faz I çalışmada
- 3 RP olgusu ve 2 kon-rod distrofi olgusu
- Tek doz intravitreal otolog kemik iliği kaynaklı MKH uygulanmış
- 10 aylık takip sonuçlarında retinada belirgin yapısal ve fonksiyonel toksisite izlenmemiştir.
- Olguların 4'ünde enjeksiyondan 1 hafta sonra en iyi düzeltilmiş görme keskinliğinde (EİDGK) 1 sıra artış olmuş ve bu artış takiplerde korunmuştur.

- Siqueira RC, Messias A, Voltarelli JC, Scott IU, Jorge R. Intravitreal injection of autologous bone marrow-derived mononuclear cells for hereditary retinal dystrophy: a phase I trial. Retina. 2011;31:1207–14. doi: 10.1097/IAE.0b013e3181f9c242.

RETİCELL-DEVAM ÇALIŞMASI

- 20 olguya intravitreal MKH uygulaması yapılmış
- 1 yıllık takipleri sonuçlanmıştır
- 3. ayda görme ile ilişkili hayat kalitesi skorunda istatistiksel anlamlı iyileşme olurken
- 12. Ayda bu skorların başlangıç değerlerine döndüğü belirtilmiştir.

- Siqueira RC, Messias A, Messias K, Arcieri RS, Ruiz MA, Souza NF, Martins LC, Jorge R. Reticell 2014. Quality of life in patients with retinitis pigmentosa submitted to intravitreal use of bone marrow-derived stem cells (Reticell -clinical trial) Stem Cell Research & Therapy 2015; 6:29 DOI 10.1186/s13287-015-0020-6.

Clinical Trials

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

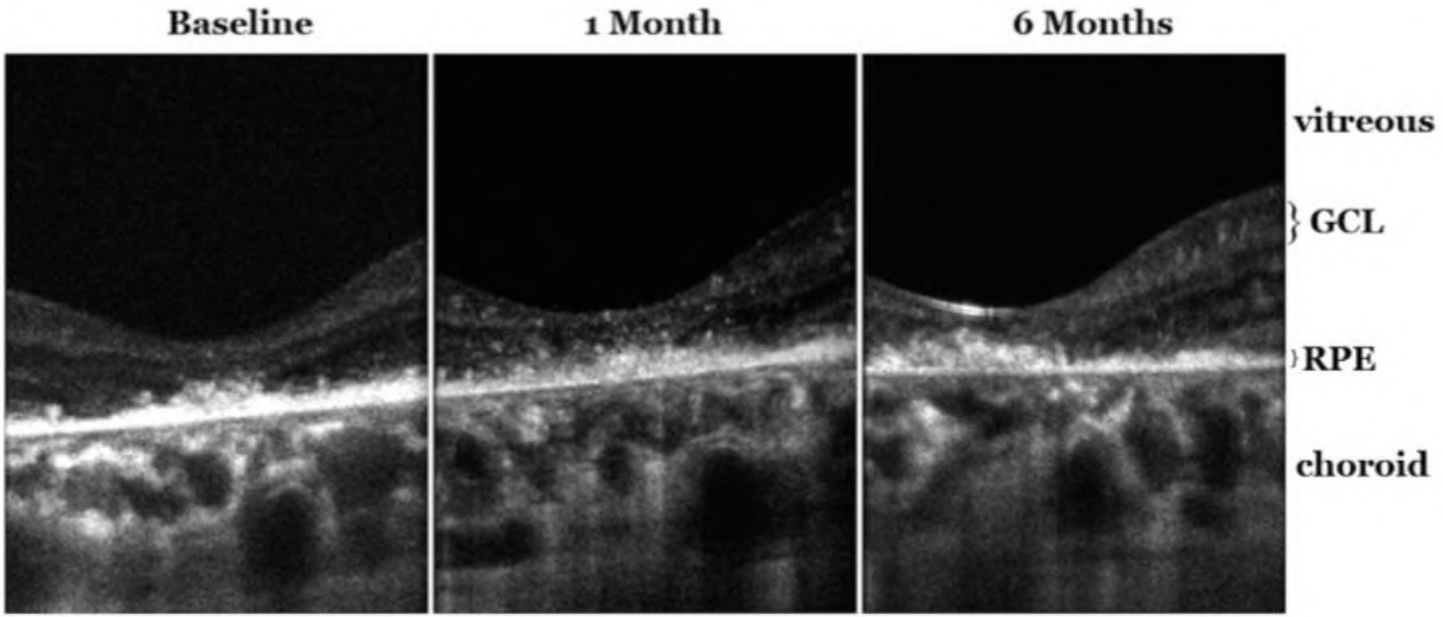
Susanna S. Park,[1] Gerhard Bauer,[2] Mehrdad Abedi,[3] Suzanne Pontow,[2] Athanasios Panorgias,[1] Ravi Jonnal,[1] Robert J. Zawadzki,[1] John S. Werner,[1] and Jan Nolta[2]

[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

- Park ve ark. geri dönüşümsüz görme kaybı olan 6 göze (retinal vasküler hastalıklar, herediter ya da noneksüdatif YBMD, RP)
- 3.4 milyon intravitreal kemik iliği kaynaklı MKH enjekte edilmiştir.
- Bu tedavi iyi tolere edilmiş, intraokuler inflamasyon ya da proliferasyona rastlanmamış
- 6 aylık takip sonrasında ERG ve EİDGK'de herhangi bir bozulma görülmemiştir.

- Park SS, Bauer G, Abedi M, Pontow S, Panorgias A, Jonnal R, Zawadzki RJ, Werner JS, Nolta J. Intravitreal autologous bone marrow CD34+ cell therapy for ischemic and degenerative retinal disorders: preliminary phase 1 clinical trial findings. Invest Ophthalmol Vis Sci. 2014;56:81–89. DOI:10.1167/iovs. 14-15415



RPE HİPERREFLEKTİVİTE ARTIŞI

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

J Ophthalmic Vis Res 2017; 12(1): 58-64

3 OLGUNUN BİRİNDE FİBRÖZ PROLİFERASYON

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]

1 olguda KNVM, 5 olguda fibröz proliferasyon

EURETINA 2018: Subretinal Adipose Tissue Derived Mesenchymal Stem Cell Implantation Shows Promise for Retinitis Pigmentosa

Mid-term outcomes highlight potential complications, however

PracticeUpdate Editorial Team

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September 21, 2018—Vienna, Austria—A 1-year follow-up of patients given subretinal injections of adipose tissue derived mesenchymal stem cells suggests the treatment may improve visual acuity, but it is not without potential ocular complications. The study was presented here at the 16th Congress of the European Society of Retina Specialists (EURETINA), which took place from September 20 to September 23.

There is currently no cure for retinitis pigmentosa, an inherited, progressive condition that leads to total blindness. One avenue currently under investigation is subretinal injection of stem cells, in an effort to replace defective or dead cells. Mesenchymal stem cells have been identified as good candidates for this therapy because of their ability to perform many functions, including immunoregulation, anti-apoptosis of neurons, and secretion of neurotrophins. Previous studies have demonstrated that mesenchymal stem cells are also able to maintain and regulate the microenvironment in different models of retinal degeneration as well as differentiate into retinal progenitor cells, photoreceptors, and retinal neural-like cells.

Ayşe Öner, MD, of Erciyes University Faculty of Medicine, Kayseri, Turkey presented a prospective case series of 14 patients with advanced stage retinitis pigmentosa who received subretinal adipose tissue derived mesenchymal stem cell implantation and were followed for 1 year after the procedure. Prior to undergoing the implantation, all patients had total visual field defects, and 7 only had light perception. The best corrected visual acuity was 20/2000. All patients had undetectable electroretinography.

Only the worse of the two eyes of each patient was operated. The procedure consisted of a total vitrectomy with 23 gauge, followed by subretinal injections of adipose tissue derived mesenchymal stem cells.

None of the patients experienced any systemic complications, and 8 patients had no ocular complications. One patient developed a choroidal neovascular membrane, which was treated with intravitreal anti-VEGF medication. The first 6 patients to undergo the procedure developed an epiretinal membrane with localized peripheral tractional retinal detachment at the periphery. This required a second vitrectomy. After 6 months, 1 of these patients developed mild band keratopathy. In another patient, retrolental fibrous tissue was found at 12 months.

To date, 4 patients have experienced visual acuity improvement.

According to the investigators, these findings offer some indication of medium-term safety of subretinal implantation of adipose tissue derived mesenchymal stem cells. It also highlights the potential ocular complications, however, suggesting the treatment should be delivered with caution.

"To optimize the cell delivery technique and to evaluate the effects of this therapy on visual acuity and the quality of life of these patients, future studies with larger number of cases will be necessary," they conclude in their abstract.

"The potential for stem cell use in the eye is very exciting to think about," Hasa Shah, MD, of Mid Atlantic Retina Specialists in Hagerstown told Elsevier's **PracticeUpdate** in a comment on the study. "The difficult part will be harnessing the good and filtering out the bad, which comes with stem cells. Retinal pigment epithelium proliferation and fibroblast formation from stem cell use is a source for proliferative vitreoretinopathy intraocularly, which can doom retinal procedures. Still, positives can be taken from this approach as we continue to march forward." Dr. Shah was not involved in the study.

Öner A, Gönen ZB, Sinim N, Çetin M, Özkul Y. Subretinal adipose-tissue derived mesenchymal stem cell implantation in advanced stage retinitis pigmentosa: A Phase I clinical safety study. Stem Cell Research and Therapy, 2016;7:178.

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.

Gelecekte…

- Retinitis pigmentosalı olgularda MKH uygulaması hastalığın ilerlemesini önlemede etkili bir tedavi seçeneği olabilir.
- Bu konuda daha çok sayıda olgu içeren çalışmalara ihtiyaç vardır.