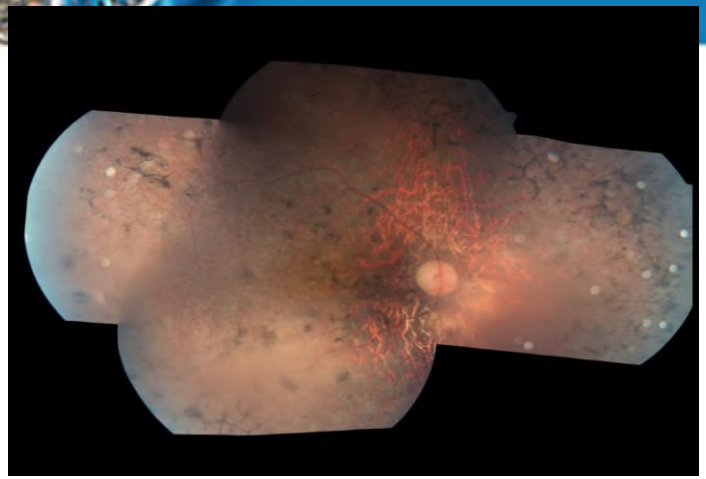
HEREDİTER RETİNA HASTALIKLARINDA

GEN VE KÖK HÜCRE TEDAVİSİ

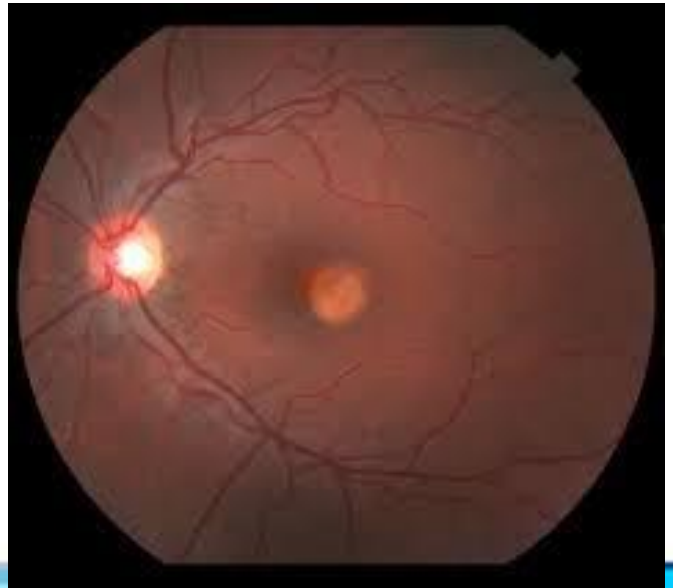
Prof.Dr. Ayşe Öner, FEBO
Erciyes Üniversitesi Tıp Fakültesi
Göz Hastalıkları AD KAYSERİ
TOD 39. Nisan Kursu
Ankara 2019

Sunumda adı geçen ürünlerle
herhangi bir finansal ilintim yoktur.

HEDEFLENEN RETİNAL HASTALIKLAR

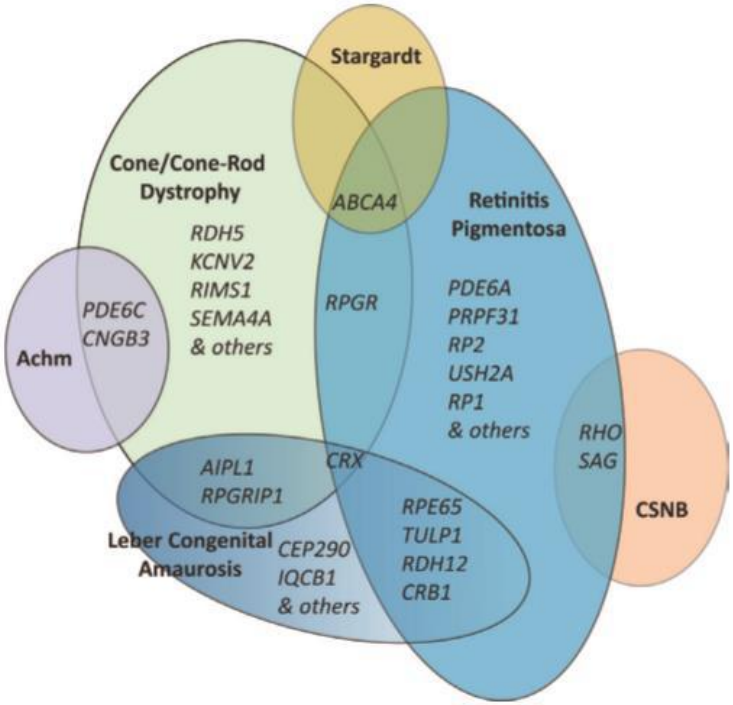


RP, Leber KA, YBMD, BEST, STARGARDTS', OPTİK NÖROPATİLER



GEN TEDAVİSİ

* Herediter retina hastalıklarında bilinen 260 dan fazla gen ve 3000 den fazla allel bulunmaktadır.



GEN TEDAVİSİ

* Hastalığa neden olan mutasyonlu geni tespit etmek gerekir.
* Bu gen bir vektöre yüklenerek göze uygulanır. (Subretinal, intravitreal)
* Vektör olarak adenovirus, lentivirus ve adeno-associated virus (AAV) kullanılabilir .
* Okuler gen tedavisinde en çok rekombinant adeno-associated virus (rAAV) kullanılmaktadır.

Vektörler	Özellikleri	Avantajları	Kısıtlamaları
AAV	-Tek sarmallı DNA içerir. -Büyüklüğü 20 nm -Parvovirustan elde edilir -Vektör DNA sı hücre DNA sıyla birleşebilir.	-Nonpatojeniktir. -Nonintegredir -Uzun süreli gen ekspresyonu mümkündür.	**-Kapasitesi küçük 4.5-4.7 kb** -Uzun süreli etki sadece postmitotik hücrelerde olur -Toplumda AAV immunitesinin yüksek olması
LV	-Tek sarmallı RNA içerir. -Büyüklüğü 120 nm -Vektör DNA sı hücre DNA sına integre olur	-**Kapasite yüksek 10 kb** -İmmunojenite düşük -Bölünen hücrelerde gen ekspresyonu mümkün	-Üretim verimi düşük -**Mutagenez riski var**
AV	-Çift sarmal DNA içerir. --Vektör DNA sı hücre DNA sıyla birleşebilir.	-**Kapasite yüksek 37 kb** -Hem bölünen hem de bölünmeyen hücrelerde gen ekspresyonu yapar	**-Çok güçlü antiviral immun yanıta yol açar** -Uzun dönemde postmitotik hücrelerde etkili
Nonviral Vektörler	Lipozom ve nanopartiküller	İmmunojenite düşüktür.	**- Etkinliği daha düşük** -Gen ekspresyonu kısa süreli

GEN TEDAVİSİ KLİNİK ÇALIŞMALAR
RPE65 Mutasyonlu LEBER KA

* RPE65 gen mutasyonu olan LKA'lu olgularda
* Subretinal RPE65 genini taşıyan rAAV2
* 3 yıllık takip
* Olguların %65'inde görme keskinliği, görme alanı ve retinal hassasiyette artış izlenmiştir.
* Gözlerin %57 sinde yan etki görülmüş.

* Jacobson SG, et al. Gene Therapy for Leber Congenital Amaurosis caused by RPE65 mutations: Safety and Efficacy in Fifteen Children and Adults Followed up to Three YearsArch Ophthalmol . 2012 January ; 130(1): 9–24.
* Testa F.et al. Three Year Follow-Up after Unilateral Subretinal Delivery of Adeno-Associated Virus in Patients with Leber Congenital Amaurosis Type2. Ophthalmology . 2013 June ; 120(6): 1283–1291
* Baainbridge JWG. Et al Long-Term Effect of Gene Therapy on Leber's Congenital Amaurosis. N Engl J Med. 2015 May 14; 372(20): 1887–1897
* Weleber RG. Results at 2 Years after Gene Therapy for RPE65-Deficient Leber Congenital Amaurosis and Severe Early-Childhood-Onset Retinal Dystrophy. Ophthalmology. 2016 Jul;123(7)

Luxturna: Voretigene Neparvovec-rzyl

* Ocak 2017 de FDA onayı aldı
* rAAV vektörüyle uygulanan bir gen tedavisidir.
* Biallelic (homozigot) RPE 65 gen mutasyonunda endike
* **Hastanın canlı retina hücreleri olması gerekir.**
* 1 yaşından büyük olgulara uygulanabilir.
* 1.5 x $10/_{11}$ vektör genomu içerir. Volum: 0.3 mL. dir.
* PPV sonrası subretinal olarak uygulanır.
* RPE65 geni RP'li olgularda %2, LKA 'lı olgularda %16

Figure 3. Injection Apparatus Assembly

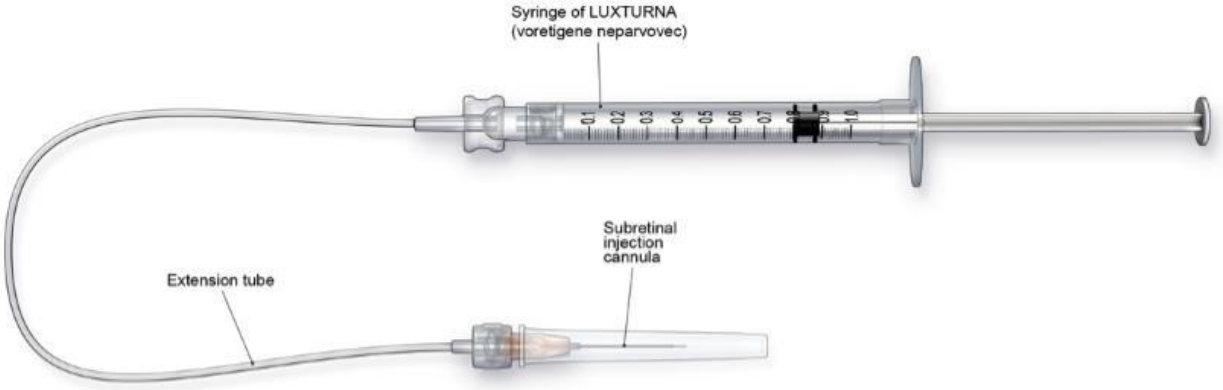


Figure 5a. Subretinal injection cannula introduced via pars plana

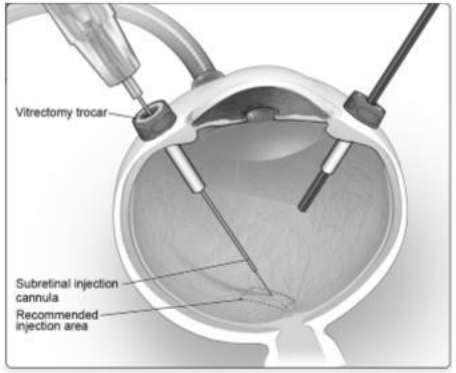
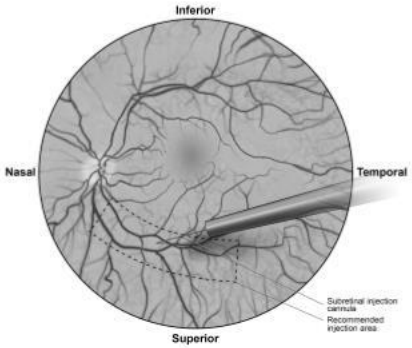


Figure 5b. Tip of the subretinal injection cannula placed within the recommended site of injection (surgeon's point of view)



Luxturna: Yan Etkiler

Table 1. Ocular Adverse Reactions Following Treatment with LUXTURNA (N=41)

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Any ocular adverse reaction	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Increased intraocular pressure	6 (15%)	8 (10%)
Retinal tear	4 (10%)	4 (5%)
Dellen (thinning of the corneal stroma)	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits*	3 (7%)	3 (4%)
Eye inflammation	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)
Eye pain	2 (5%)	2 (2%)
Maculopathy (wrinkling on the surface of the macula)	2 (5%)	3 (4%)
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Foveal dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

*Transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site 1-6 days after injection

Gen Tedavisiyle İlgili Çalışmalar

Table I Summary of Active Ocular Gene Therapy Programs

Company	Program/ Product	Disease/ Mechanism	Vector Technology	Administration Route	Status	References
Spark Therapeutics, Inc.	LUXTURNA™ (voretigene neparvovec-rzyl)	Confirmed biallelic RPE65 mutation–associated retinal dystrophy; *RPE65* gene delivery	AAV2	Subretinal injection	US approval (2017)	Prescribing information
Nightstar Therapeutics	NSR-REP1	Choroideremia; *REP1* gene delivery	AAV2	Subretinal injection	Phase III	Company website NCT03496012
	NSR-RPGR	X-linked retinitis pigmentosa; codon-optimized *RPGR* gene delivery	AAV	Subretinal injection	Phase I/II	Company website NCT03116113
	NSR-BEST1	Best vitelliform macular dystrophy; *BEST1* gene delivery	Undisclosed	Undisclosed	Preclinical	Company website
RegenXBio Inc.	RGX-314	Wet AMD; anti-VEGF monoclonal antibody fragment	NAV AAV8	Subretinal injection	Phase I	Company website
Applied Genetic Technologies Corporation	XLRS (with Biogen, Inc.)	X-linked retinoschisis; *hRS1* gene delivery	rAAV2tYF	Intravitreal injection	Phase I/II	April 10, 2018 press release
	ACHM B3	Achromatopsia; *hCNGB3* gene delivery	rAAV2tYF	Subretinal injection	Phase I/II	Company website NCT02599922
	ACHM A3 / AGTC-402	Achromatopsia; *hCNGA3* gene delivery	rAAV2tYF	Subretinal injection	Phase I/II	Company website NCT02935517
	XLRP (with Biogen, Inc.)	X-linked retinitis pigmentosa; *RPGR* gene delivery	rAAV2tYF	Subretinal injection	Phase I/II	April 18, 2018 press release
GenSight Biologics	GS010 (rAAV2/2-ND4)	LHON	AAV2	Intravitreal injection	Phase I/II	NCT02064569
National Eye Institute, US National Institutes of Health	scAAV2-P1ND4v2	LHON	AAV2	Intravitreal injection	Phase I	NCT02161380
Sanofi Genzyme	SAR422459 (with Oxford BioMedica)	Stargardt disease; *ABCR* gene delivery	Lentivirus (LentiVector)	Subretinal injection	Phase II	Company website
	SAR421869 (with Oxford BioMedica)	Usher syndrome type 1B; *MYO7A* gene delivery	Lentivirus (LentiVector)		Phase I/II	Company website
Allergan plc	RST-001 (acquired RetroSense Therapeutics LLC)	Retinitis pigmentosa; channelrhodopsin-2 optogenetic gene therapy	Undisclosed	Intravitreal injection	Phase I/II	Press releases NCT02556736
Oxford BioMedica	OXB-201	Wet AMD; endostatin and angiostatin gene delivery	Lentivirus (LentiVector)	Subretinal injection	Phase I	Company website
	OXB-202	Corneal graft rejection; endostatin and angiostatin gene delivery	Lentivirus (LentiVector)	Treatment of cornea prior to transplantation	Preclinical	Company website
National Eye Institute, US National Institutes of Health	RS1 AAV vector	XLRS; *RS1* gene delivery	AAV8	Intravitreal injection	Phase I/IIa	NCT02317887
Eyevensys	EYS606	Noninfectious uveitis; anti–tumor necrosis factor-α plasmid delivery	EyeCET (electrotransfection)	Ciliary muscle transfection	Phase I/II	Company website
	EYS609	Retinal vein occlusion/diabetic macular edema/wet AMD; anti-VEGF plasmid delivery	EyeCET (electrotransfection)	Ciliary muscle transfection	Preclinical	Company website
	EYS611	Retinal degeneration; neurotrophic factor plasmid delivery	EyeCET (electrotransfection)	Ciliary muscle transfection	Preclinical	Company website

Springer

EN ÇOK ÇALIŞILAN GENLER VE HASTALIKLAR

* MERTK (mer proto-onkogen tirozin kinaz) mutasyonu bulunan OR- RP
* RHO gen mutasyonu bulunan RP
* CHM mutasyonu bulunan X- R koroideremi
* ABCA4 mutasyonu olan Stargardts' distrofisi
* BEST 1 mutasyonu olan Best Distrofisi
* MYO7A mutasyonu olan Usher Sendromu
* Anti VEGF gen bileşenlerine bakılarak yaş tip YBMD tedavisi (fms like tirozin kinaz 1 (sFlt-1)) üzerinde çalışılmaktadır.

Research Paper

Phase 2a Randomized Clinical Trial: Safety and Post Hoc Analysis of Subretinal rAAV.sFLT-1 for Wet Age-related Macular Degeneration

Ian J. Constable [a,b,c], Cora M. Pierce [a], Chooi-May Lai [a,c], Aaron L. Magno [a], Mariapia A. Degli-Esposti [a,c], Martyn A. French [d,e], Ian L. McAllister [a,b,c], Steve Butler [f], Samuel B. Barone [f], Steven D. Schwartz [g], Mark S. Blumenkranz [h], Elizabeth P. Rakoczy [a,c,*]

ABSTRACT

Background: We present the results of a Phase 2a randomized controlled trial investigating the safety, and secondary endpoints of subretinal rAAV.sFLT-1 gene therapy in patients with active wet age-related macular degeneration (wAMD).

Methods: All patients (n = 32), (ClinicalTrials.gov; NCT01494805), received ranibizumab injections at baseline and week 4, and thereafter according to prespecified criteria. Patients in the gene therapy group (n = 21) received rAAV.sFLT-1 (1×10^{11} vg). All patients were assessed every 4 weeks to the week 52 primary endpoint.

Findings: Ocular adverse events (AEs) in the rAAV.sFLT-1 group were mainly procedure related and self-resolved. All 11 phakic patients in the rAAV.sFLT-1 group showed progression of cataract following vitrectomy. No systemic safety signals were observed and none of the serious AEs were associated with rAAV.sFLT-1. AAV2 capsid was not detected and rAAV.sFLT-1 DNA was detected transiently in the tears of 13 patients. ELISPOT analysis did not identify any notable changes in T-cell response. In the rAAV.sFLT-1 group 12 patients had neutralizing antibodies (nAb) to AAV2. There was no change in sFLT-1 levels in bodily fluids. In the rAAV.sFLT-1 group, Best Corrected Visual Acuity (BCVA) improved by a median of 1.0 (IQR: −3.0 to 9.0) Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline compared to a median of −5.0 (IQR: −17.5 to 1.0) ETDRS letters change in the control group. Twelve (57%) patients in the rAAV.sFLT-1 group maintained or improved vision compared to 4 (36%) in the control group. The median number of ranibizumab retreatments was 2.0 (IQR: 1.0 to 6.0) for the gene therapy group compared to 4.0 (IQR: 3.5 to 4.0) for the control group.

Interpretation rAAV.sFLT-1 combined with the option for co-treatment appears to be a safe and promising approach to the treatment of wAMD.

Funding: National Health and Medical Research Council of Australia (AP1010405), Lions Eye Institute, Perth Australia, Avalanche Biotechnologies, Menlo Pk, CA, USA.

© 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Ranibizumab ile beraber verilmiş, GK de artış ve RBZ enjeksiyon sayısında azalma sağlamış

Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial

Robert E MacLaren, Markus Groppe, Alun R Barnard, Charles L Cottriall, Tanya Tolmachova, Len Seymour, K Reed Clark, Matthew J During, Frans P M Cremers, Graeme C M Black, Andrew J Lotery, Susan M Downes, Andrew R Webster, Miguel C Seabra

Summary

Background Choroideremia is an X-linked recessive disease that leads to blindness due to mutations in the *CHM* gene, which encodes the Rab escort protein 1 (REP1). We assessed the effects of retinal gene therapy with an adeno-associated viral (AAV) vector encoding REP1 (AAV.REP1) in patients with this disease.

Methods In a multicentre clinical trial, six male patients (aged 35–63 years) with choroideremia were administered AAV.REP1 ($0{\cdot}6–1{\cdot}0\times10^{10}$ genome particles, subfoveal injection). Visual function tests included best corrected visual acuity, microperimetry, and retinal sensitivity tests for comparison of baseline values with 6 months after surgery. This study is registered with ClinicalTrials.gov, number NCT01461213.

Findings Despite undergoing retinal detachment, which normally reduces vision, two patients with advanced choroideremia who had low baseline best corrected visual acuity gained 21 letters and 11 letters (more than two and four lines of vision). Four other patients with near normal best corrected visual acuity at baseline recovered to within one to three letters. Mean gain in visual acuity overall was 3·8 letters (SE 4·1). Maximal sensitivity measured with dark-adapted microperimetry increased in the treated eyes from 23·0 dB (SE 1·1) at baseline to 25·3 dB (1·3) after treatment (increase 2·3 dB [95% CI 0·8–3·8]). In all patients, over the 6 months, the increase in retinal sensitivity in the treated eyes (mean 1·7 [SE 1·0]) was correlated with the vector dose administered per mm² of surviving retina (r=0·82, p=0·04). By contrast, small non-significant reductions (p>0·05) were noted in the control eyes in both maximal sensitivity (–0·8 dB [1·5]) and mean sensitivity (–1·6 dB [0·9]). One patient in whom the vector was not administered to the fovea re-established variable eccentric fixation that included the ectopic island of surviving retinal pigment epithelium that had been exposed to vector.

Interpretation The initial results of this retinal gene therapy trial are consistent with improved rod and cone function that overcome any negative effects of retinal detachment. These findings lend support to further assessment of gene therapy in the treatment of choroideremia and other diseases, such as age-related macular degeneration, for which intervention should ideally be applied before the onset of retinal thinning.

6 hastada ortalama 3.8 harf artış, retinal sensitivite artışı

GEN TEDAVİSİNDE ZORLUKLAR

* Herediter retina hastalıklarında bilinen 260 dan fazla gen ve 3000 den fazla allel bulunmaktadır.
* Aynı aile içinde aynı genin farklı mutasyonları söz konusu olabilmektedir.
* Bu durum hastalıkla ilgili değerlendirmeleri karmaşık hale getirmektedir.
* Yeni teknolojik gelişmelere rağmen test edilen hastaların yaklaşık %50 'sinde genetik bozukluk tespit edilebilmektedir.
* Ayrıca bu test ve tedaviler oldukça maliyetlidir. Luxturna: 425 bin dolar

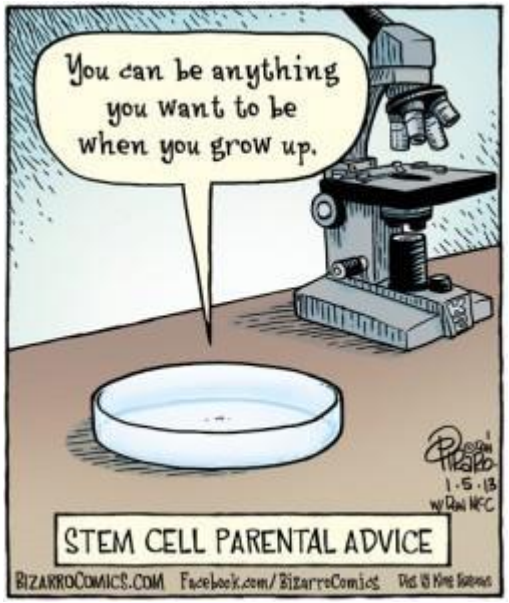
Gelecekte gen tedavisi

* Gelecekte GENOM EDİTİNG sistemleri
* CRİSPR-Cas 9: Clustered Regulatory İnterspaced Short Palindromic Repeats
* TALEN: Transcription Activator-like Effector Nucleases

KÖK HÜCRE NEDİR?

Kök Hücre:

* Hücrenin özelleşmemiş en temel ve saf halidir.
* Vücuttaki pek çok hücre tipine differensiye olabilir.
* Hasarlı hücre ve dokuları onarabilir.

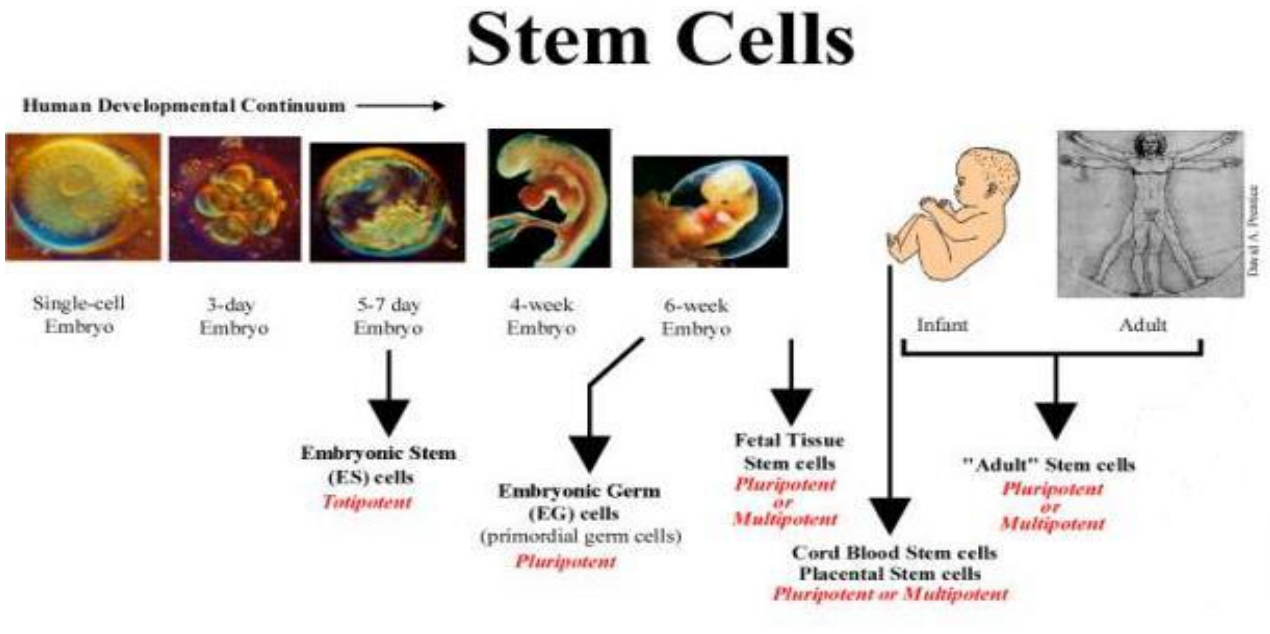


KÖK HÜCRE TİPLERİ

1- EMBRYONİK KÖK HÜCRE

2- ERİŞKİN KÖK HÜCRE

- Mesenkimal KH (Adipoz, Kemik iliği, Umblikal kord)
- İndüklenmiş pluripotent KH (İPKH)



KÖK HÜCRE TEDAVİSİNİN MEKANİZMASI

* (1) Hücre Replasmanı: Sağlıklı kök hücreler dejenere hücrelerin yerini alabilir.
* (2) Nutrisyonel Destek (Parakrin etki): Sağlıklı kök hücreler salgıladıkları faktörlerle etraftaki hücrelerin yaşamlarını desteklerler.
* (3) İmmunmodülator etki

KÖK HÜCRE TEDAVİSİNİN MEKANİZMASI

* **(2) Nutrisyonel Destek:** Sağlıklı kök hücreler salgıladıkları faktörlerle etraftaki hücrelerin yaşamlarını desteklerler (Parakrin, Trofik etki)
* Proangiogenik faktörler: Angiogenin, PLGF
* Angiogenik kemokinler: CXCL1, CXCL,CXCL5,CXCL6 ve CXCL8
* Angiogenik growth faktörler: HGF, bFGF, VEGF-D, PDGF-AA, TGF-β2, G-CSF, TGF-β2
* Nörotrofik faktörler: bFGF, nerve growth factor (NGF), neurotrophin 3 (NT3), neurotrophin 4 (NT4), glial-derived neurotrophic factor (GDNF)
* Hematopoietik growth faktörler: G-CSF, GM-CSF, LIF, IL-1α, IL-6, IL-8, and IL-11.

Gözde Kök Hücre Kullanımı

* Çok küçük dozlar yeterli olur.
* Cerrahi yaklaşım kolaydır.
* Nakledilen hücre kolayca izlenir.
* Gözün immün yapısı uygundur.
* Ekstraoküler yayılım söz konusu değildir.

KÖK HÜCRE İLE İLGİLİ YAYINLAR

- Schwartz SD, Regillo CD, Lam BL, et al. 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. *Lancet* 2015;385:509-16.
- Song WK, Park KM, Kim HJ, et al. Treatment of macular degeneration using embryonic stem cell-derived retinal pigment epithelium: preliminary results in Asian patients. *Stem Cell Reports* 2015;4:860-72.
- 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;7:46913-23.
- Mandai M, Watanabe A, Kurimoto Y, et al. Autologous Induced Stem-Cell-Derived Retinal Cells for Macular Degeneration. *N Engl J Med* 2017;376:1038-46
- Kuriyan AE, Albini TA, Townsend JH, et al. Vision Loss after Intravitreal Injection of Autologous "Stem Cells" for AMD. *N Engl J Med* 2017;376:1047-53.
- Kumar A, Midha N, Mohanty S, Chohan A, Seth T, Gogia V, Gupta S.Evaluating role of bone marrow-derived stem cells in dry age-related macular degeneration using multifocal electroretinogram and fundus autofluorescence imaging. *Int J Ophthalmol.* 2017;10(10), 1552-1558.
- Siqueira RC, Messias A, Messias K, et al. 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.
- Park SS, Bauer G, Abedi M, et al. Intravitreal autologous bone marrow CD34+ cell therapy for ischemic and degenerative retinal disorders: preliminary phase 1 clinical trial findings. *Invest Ophthalmol Vis Sci* 2015;56:81-9.
- Satarian L, Nourinia R, Safi S, et al. Intravitreal Injection of Bone Marrow Mesenchymal Stem Cells in Patients with Advanced Retinitis Pigmentosa; a Safety Study. *J Ophthalmic Vis Res* 2017;12:58-64.
- **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;7:178.**
- **Oner A, Gonen ZB, Sevim DG, Sinim 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. Cellular Reprogramming. 2018; 20(6):329-336. DOI: 10.1089/cell.2018.0045**
- Weiss JN, Levy S. Stem Cell Ophthalmology Treatment Study: bone marrow derived stem cells in the treatment of retinitis pigmentosa. *Stem Cell Investig*. 2018 Jun 6;5:18.
- 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;11:1685-94.
- 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.

Klinik Çalışmalar-MKH

* 6 gözde 6 aylık takip
* Enflamasyon ve tümör oluşumu yok
* Hepsinde görme artışı
* 1 olguda KNVM

* Invest Ophthalmol Vis Sci. 2014 Dec 9;56(1):81-9. Intravitreal autologous bone marrow CD34+ cell therapy for ischemic and degenerative retinal disorders: preliminary phase 1 clinical trial findings. Park SS et al .

* 20 RP olgusu intravitreal Kİ-derive KH
* KMÖ de de düzelme
* 3 ayda görme artışı, 1 yılda eskiye dönüş
* Okuler ve sistemik komplikasyon yok

* Siqueira et al. Stem Cell Research & Therapy (2015) 6:29 Quality of life in patients with retinitis pigmentosa submitted to intravitreal use of bone marrow-derived stem cells (Reticell -clinical trial)

Siqueira, R.C.; et al. Resolution of macular oedema associated with retinitis pigmentosa after intravitreal use of autologous BM-derived hematopoietic stem cell transplantation. Bone Marrow Trans. 2013, 48, 612–613

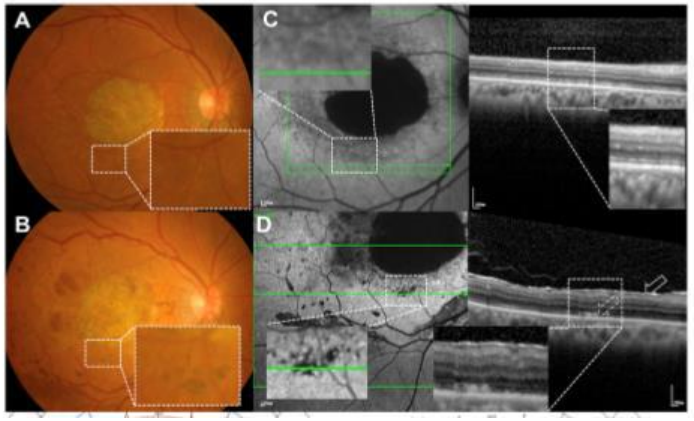
Klinik Çalışmalar -EKH

* Faz1-2 prospektif çalışma subretinal hEKH-derived RPE
* 9 Stargardt's makula distrofisi ve 9 kuru tip AMD.
* Toplam 18 olgu ortalama 22 ay takip
* 10 gözde görme keskinliğinde artış
* 13 (72%) gözde subretinal pigmentasyonda artış
* Görme ile ilişkili hayat kalitesinde artış

* Schwartz SD et al. 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. Lancet. 2015 Feb 7;385(9967):509-16.

* 4 AMD, 4 SMD olgusu 1 yıl takip
* İnflamasyon ve okuler komplikasyon
* 1 olguda KNVM ve ERM
* 1 yılda tüm olgularda görme artışı

* Song WK et al. Stem Cell Reports. 2015 May 12;4(5):860-72.Epub 2015 Apr 30. Treatment of macular degeneration using embryonic stem cell-derived retinal pigment epithelium: preliminary results in Asian patients.



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.

NEURAL REGENERATION RESEARCH
October 2016, Volume 11, Issue 10
www.nrronline.org

RESEARCH ARTICLE

Stem Cell Ophthalmology Treatment Study (SCOTS): bone marrow-derived stem cells in the treatment of Leber's hereditary optic neuropathy

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

1 Retina Associates of South Florida, 5800 Colonial Drive, Suite 300, Margate, FL, USA
2 MD Stem Cells, 3 Sylvan Road South, Westport, CT, USA
3 The Eye Center of Columbus, The Ohio State University, Columbus, OH, USA

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]

KLİNİK ÇALIŞMALARIM

ÜLKEMİZDE KÖK HÜCRE UYGULAMALARI

* İnsan embriyonik kök hücre kullanımı yasaktır (2005)

* Erişkin kök hücre ve İPKH kullanımı için ise Lokal Etik Kurumdan ve Sağlık Bakanlığı'ndan (Doku, Organ ve Kök Hücre nakli birimi) onay gereklidir.

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]

Etkili ancak komplikasyon oranı yüksek

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

Save | Recommend | Share | Get Topic Alerts

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.

Ayse 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 8 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.

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].

25 OLGUNUN 36 GÖZÜ
KURU TİP YBMD
SUPRAKOROİDAL ADMKH

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.

FAZ II ÇALIŞMAMIZ

* Çalışma için kurumun etik kurulundan (No:2017/480) ayrıca T.C Sağlık Bakanlığı bünyesinde bulunan Organ Doku ve Diyaliz Hizmetleri Daire Başkanlığı'ndan (No: 56733164/203) onay alınmıştır.

* 20 olgu opere edildi. (YBMD, RP, Stargardt MD, optik atrofi)

* Suprakoroidal olarak adipoz dokudan derive edilmiş allojenik mezenkimal KH kullanıldı.

CELLULAR REPROGRAMMING
Volume 20, Number 6, 2018
© Mary Ann Liebert, Inc.
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]

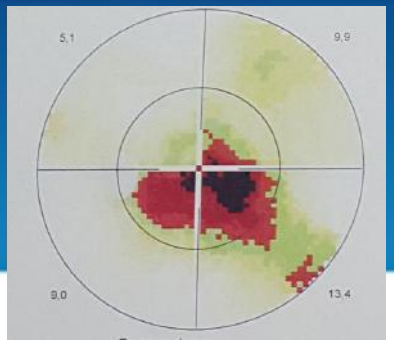
SONUÇLAR

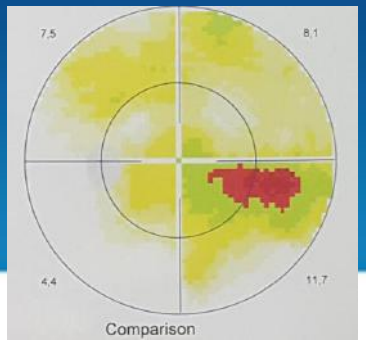
* 20 olgunun 1 yıllık takipleri tamamlanmıştır.
* Hiçbir olguda sistemik komplikasyon olmadı.
* Hiçbir olguda okuler komplikasyon olmamıştır.

SUPRAKOROİDAL KÖK HÜCRE UYGULAMASI GÜVENLİ

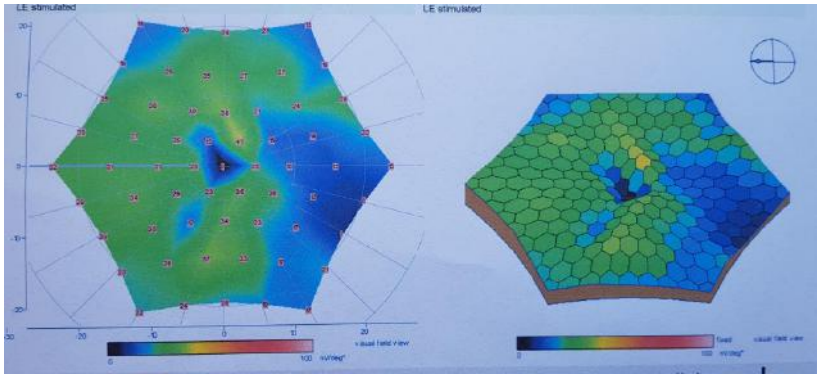
SONUÇLAR

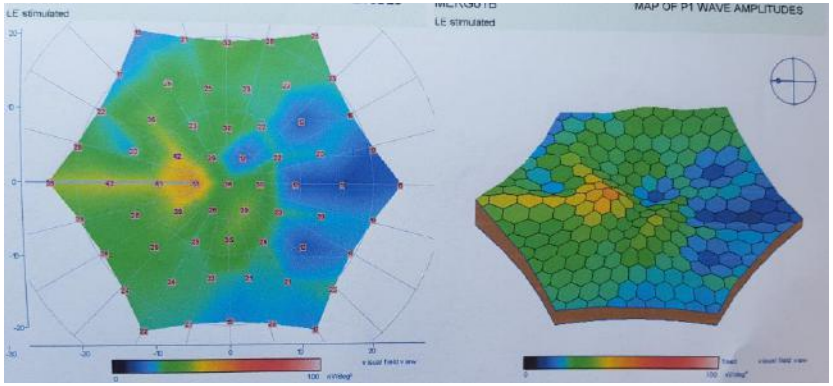
* Olguların % **85'inde** değişen düzeylerde görme keskinliği ve görme kalitesi artışları saptanmıştır. %15'i stabil seyretmiştir.
* Preop görmesi iyi olan olgularda görme artışı da fazladır.
* Görme artışı 1. ay kontrolünde başlamış, 6 ay ve 1 yıl kontrolünde daha da belirginleşmiştir.
* Olguların hepsinde mf ERG ve PGA testlerinde iyileşme saptanmıştır.
* SUPRAKOROİDAL KÖK HÜCRE UYGULAMASI ETKİLİ

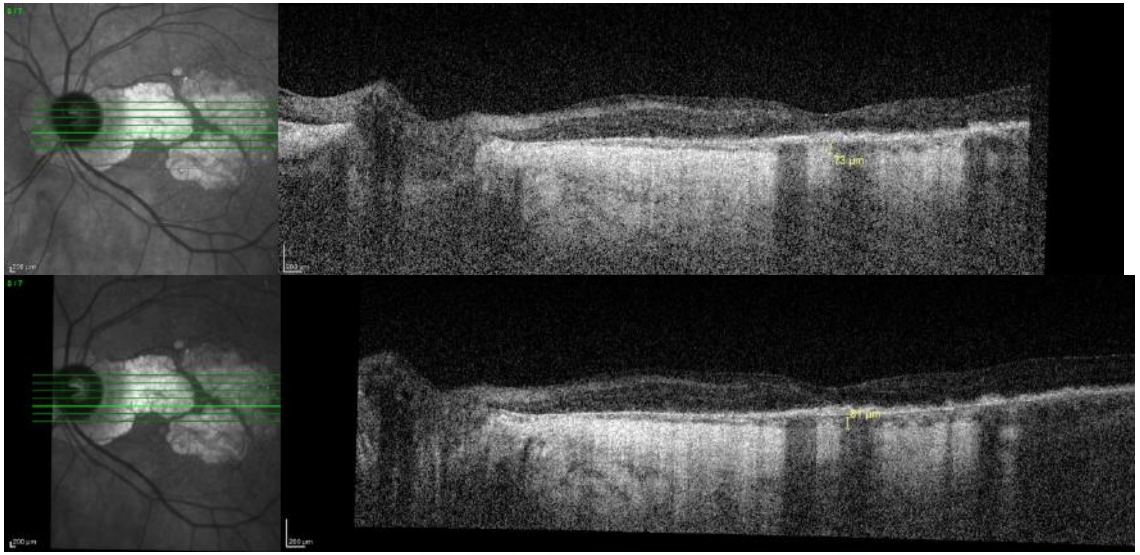




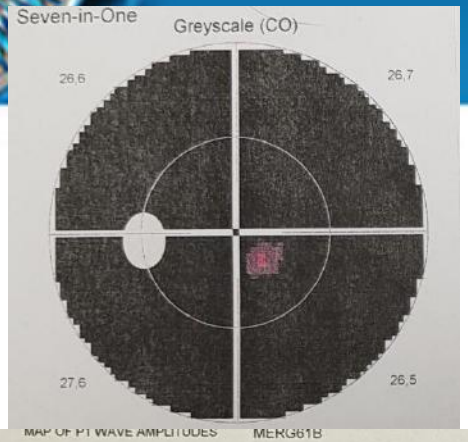
Kuru Tip YBMD olgusu GK: 1 mps den 0.05 e yükselmiştir.



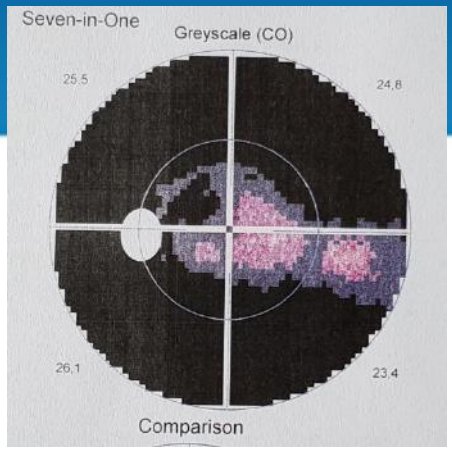


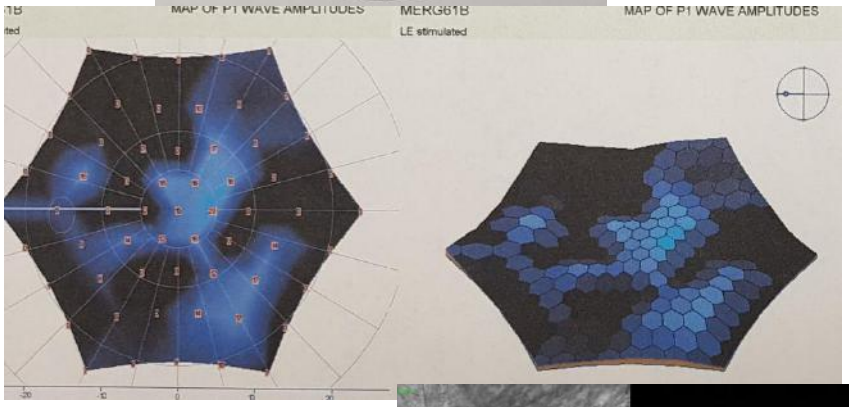


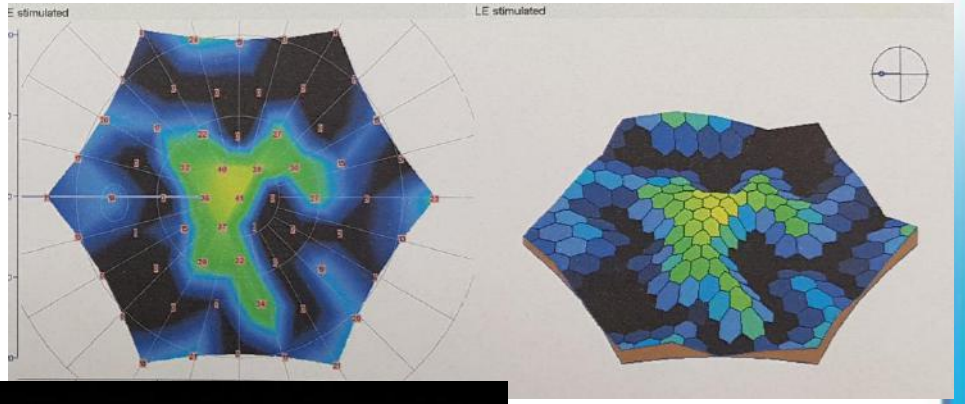
OLGU: RETİNİTİS PİGMENTOSA

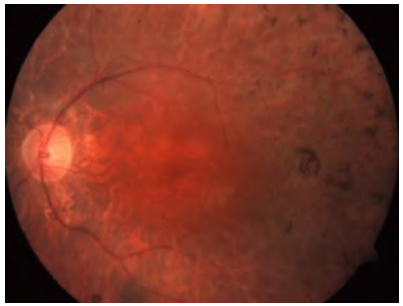


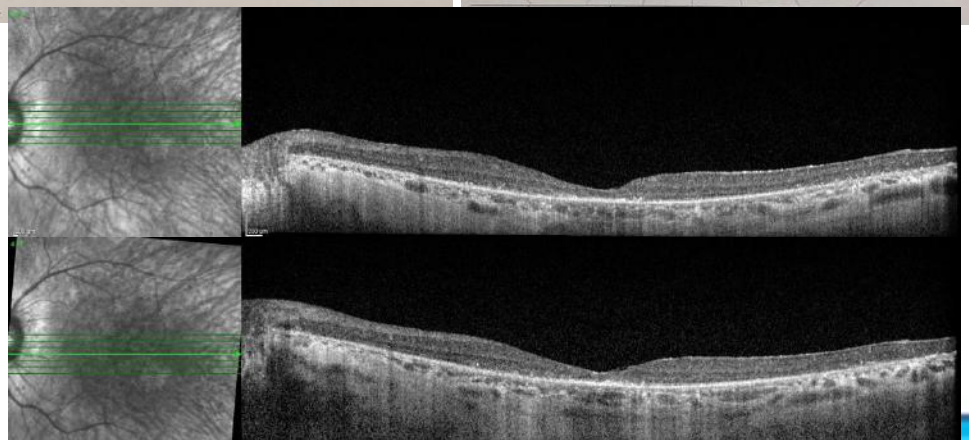
57 y kadın olgu
GK: 1 meh'den 2 mps'ye

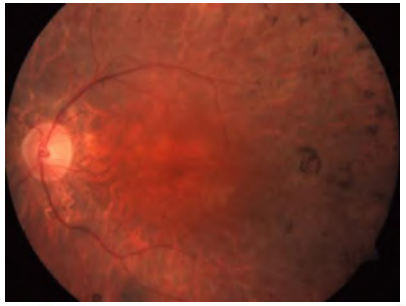












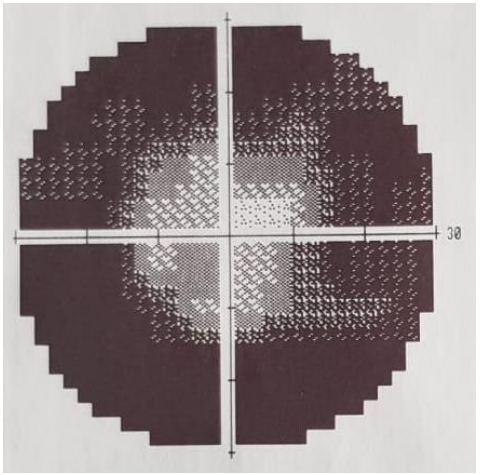
FAZ II SONRASINDA

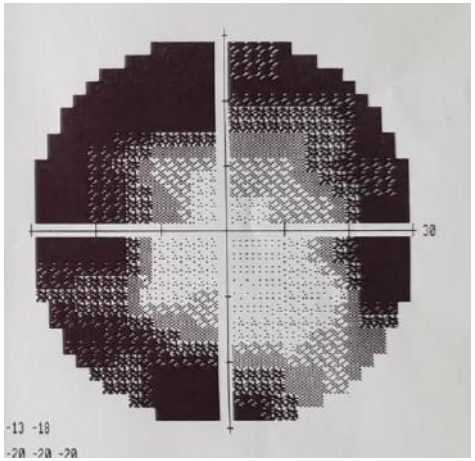
* Önce 23 kişilik grup

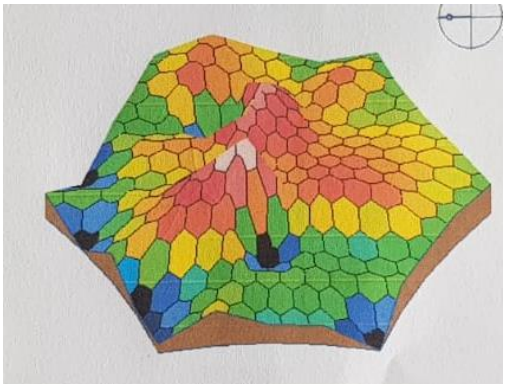
* Daha sonra da 100 kişilik grup için onay alınmıştır.

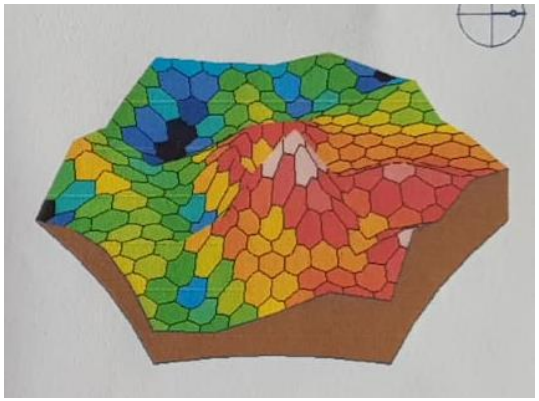
Suprakoroidal umblikal kord kaynaklı MKH

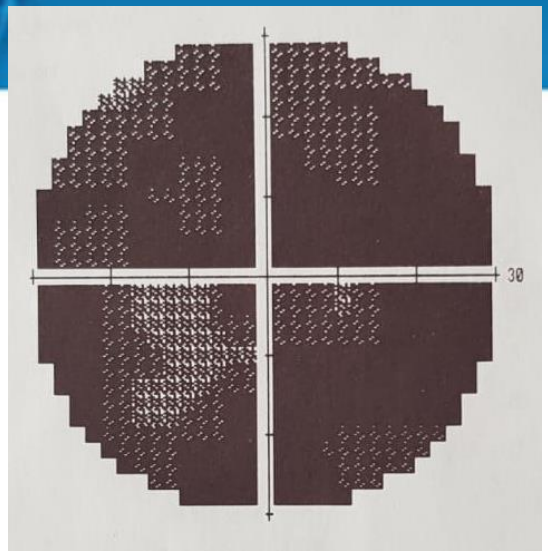
48 y, Kadın RP'li olgu Sol göz tedavi edildi GK: 0.4'ten 0.6 ya yükseldi

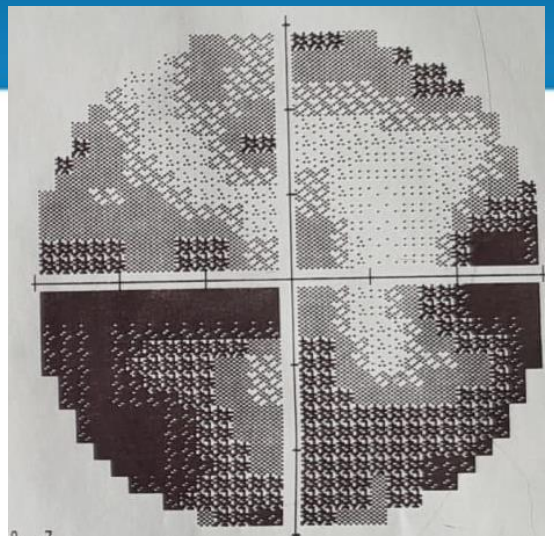




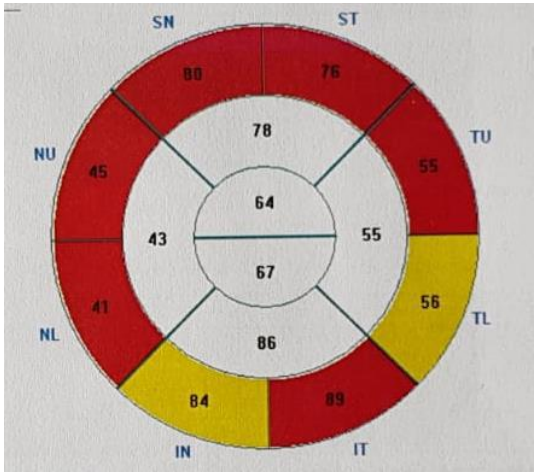


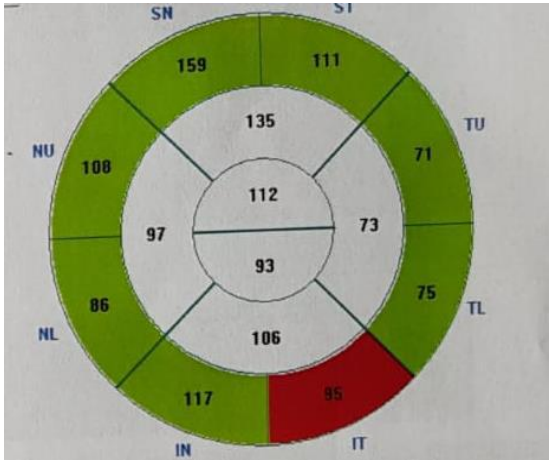






45 y erkek olgu, kafa travması sonrası optik atrofi sağ : p(-) Sol 0.4'ten 0.7'e yükseldi





STANDART PROTOKOL?

* Hangi KH'yi kullanmalı? Ülkemizde MKH
* Hangi dozda kullanmalı? 2-4 milyon
* Hangi şekilde uygulamalı: Subretinal, intravitreal, suprakoroidal, intravenöz?
* Etkisi ne kadar sürecek?
* Ülkemizde ve pek çok ülkede uygulama için etik onay, Sağlık Bakanlığı onayı istenmektedir.

MESAJLAR

TEŞEKKÜR EDERİM