Intravitreal Injection of Allogeneic Human Retinal Progenitor Cells for Treatment of Retinitis Pigmentosa: Results from the Phase 2b Trial

- Anthony Joseph, MD
- David S. Boyer, MD
- Baruch D. Kuppermann, MD, PhD
- Jeffrey S. Heier, MD
- Peter K. Kaiser, MD
- David S Liao, MD, PhD
- Mitul C Mehta, MD MS
- Rebecca Kammer, OD, PhD
- Bonnie J Mills, PhD
- Jing Yang, MD, PhD
- Henry J Klassen, MD, PhD

OBJECTIVE To assess efficacy and safety of intravitreal injection of allogeneic human retinal progenitor cells (hRPC) as compared to sham in adult subjects with retinitis pigmentosa.

PURPOSE Allogeneic human retinal progenitor cells (hRPCs) secrete neurotrophic factors that promote retinal photoreceptor cell survival and function. This paracrine mechanism has shown promise as a therapeutic strategy for retinitis pigmentosa (RP), a hereditary blinding disease. A phase 2b trial was conducted to evaluate intravitreal injection of an allogeneic hRPC for treatment of RP.

METHODS Patients with RP and best-corrected visual acuity (BCVA) between 20/80 and 20/800 were randomized to treatment versus sham. Treatment consisted of 3.0x106 or 6.0x106 hRPCs via a single intravitreal injection. The primary efficacy endpoint was mean change in BCVA at month 12. Secondary endpoints included a low light mobility test, contrast sensitivity, kinetic visual fields, and a vision function questionnaire. In a post hoc

exploratory analysis, the primary and secondary endpoints were assessed in a target subgroup of patients with baseline central fixation, without constricted field (≥12° diameter), and study eye did not have significantly worse BCVA than their fellow eye (≤15 letters).

RESULTS A total of 84 patients were randomized; 3 were lost to follow-up and 2 were excluded from efficacy analysis for protocol violations. Mean changes in BCVA from baseline to month 12 were +2.63, +1.27, and +5.95 letters in the sham arm (N=27), 3.0x106 hRPC (N=26), and 6.0x106 hRPC (N=26) treatment arms, respectively. In the post hoc exploratory analysis of the target subgroup, mean changes in BCVA from baseline to month 12 were +1.57, -0.15, and +13.05 letters in the sham arm (N=14), 3.0x106 hRPC (N=13), and 6.0x106 hRPC (N=13) treatment arms, respectively (p=0.012 for 6.0x106 hRPCs vs sham). Improvements in the 6.0x106 group were found in all other secondary endpoints. Most adverse events were minor and transient; there was one serious adverse event in the 3.0x106 hRPC arm of grade-3 ocular hypertension that resolved with treatment.

CONCLUSION Intravitreal injection of hRPCs is a novel approach for treatment of RP, agnostic of the genetic subtype. This phase 2b study demonstrates favorable biological activity and an excellent safety profile, warranting progression to phase 3 trials.

HUMAN RESEARCH Yes: Approved by institutional review board

Genetic profile and Associated Characteristics of 265 Korean Patients with Retinitis Pigmentosa.

- Young Hee Yoon, MD, PhD
- Yoon Jeon Kim, MD
- Joo Yong Lee, MD
- You Na Kim, MD
- Eul-Ju Seo, MD
- Beom Hee Lee

OBJECTIVE A comprehensive molecular analysis of 265 Korean patients with retinitis pigmentosa to identify the distribution of the causative genetic mutations in Korean.

PURPOSE Because of genotype-phenotypes heterogeneity of retinitis pigmentosa(RP), the identification of causative genes is critical. Since more than 73 causative genes are known in RP, targeted next-generation sequencing(NGS) or whole exome sequencing (WES) offers effective methods for molecular analysis. With targeted NGS or WES, we analyzed genetic profiles and associated characteristics in Korean RP.

METHODS We performed prospective analysis of 265 Korean patients diagnosed with RP who visited the single tertiary clinic from November 2018 to November 2019. The diagnosis of RP was screened by retinal specialists based on comprehensive clinical history taking including pedigree analysis as well as ophthalmologic examinations. Targeted NGS consists of 88 genes associated with RP was performed in 156 patients and WES was performed in 66 patients. Also, 43 of 74 patients revealed to have no pathogenic variant or variants unknown significance were re-examined by WES to identify causative genes.

RESULTS From 124 nonsyndromic RP(nsRP) and 8 syndromic RP(sRP) cases, the mean age was 48.3 and 37 causative genes from 132 cases(49.8%) were identified. 82 of 156(52.6%), 34 of 66 cases(51.6%) were revealed to have causative genes by targeted NGS and WES, respectively. Among 43 cases with negative results in targeted NGS re-examined by WES, 16 (37.2%) were positive in WES. From all subjects, 33 family members of 14 families were

screened and 26 members of 12 families shared same variants. Thirty-three out of 37 genes were nsRP-causing and 4 genes were sRP-causing genes. Among nsRP, autosomal recessive RP(arRP) was the most frequent(66.1 %) and autosomal dominant RP(adRP) was 30.6%. The three most common genes were USH2A(8%), EYS(7%), PDE6B(5%), and all are arRP related. Whereas patients with USH2A, EYS mutations underwent the first visual symptoms at the median age of 32.5 and 21.0, patients with PDE6B experienced earlier symptoms at the age of 10 and develop cystoid macular edema frequently.

CONCLUSION Targeted NGS and WES improved the diagnostic yield in RP. The genetic spectrum of Korean RP from this study was similar to previous studies from other East-Asian populations. Genotype-phenotype correlations would help to understand and predict the clinical course of RP.

HUMAN RESEARCH Yes: Approved by institutional review board

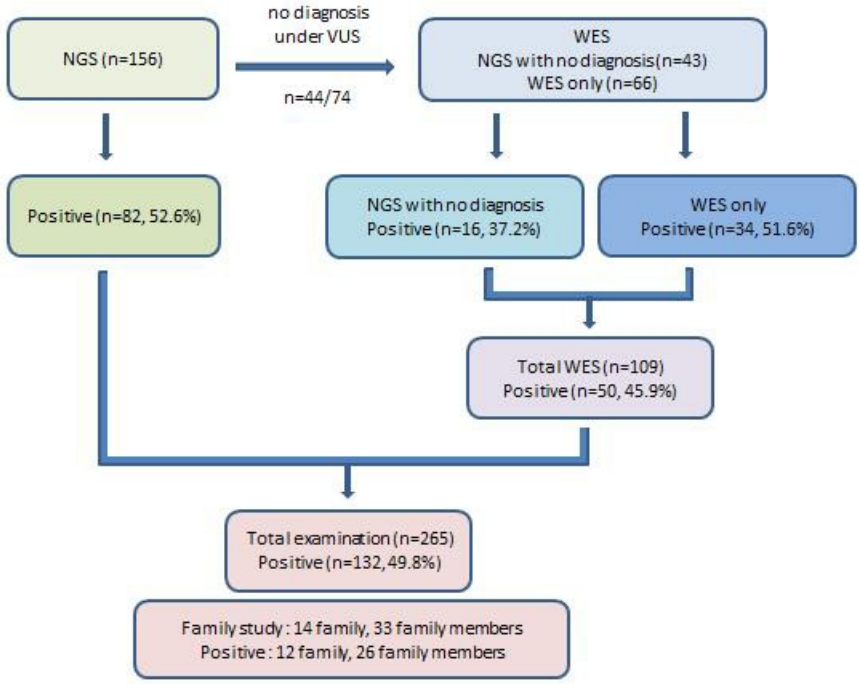

Figure 1. A flowsheet for the study of 265 Korean patients with retinitis pigmentosa.

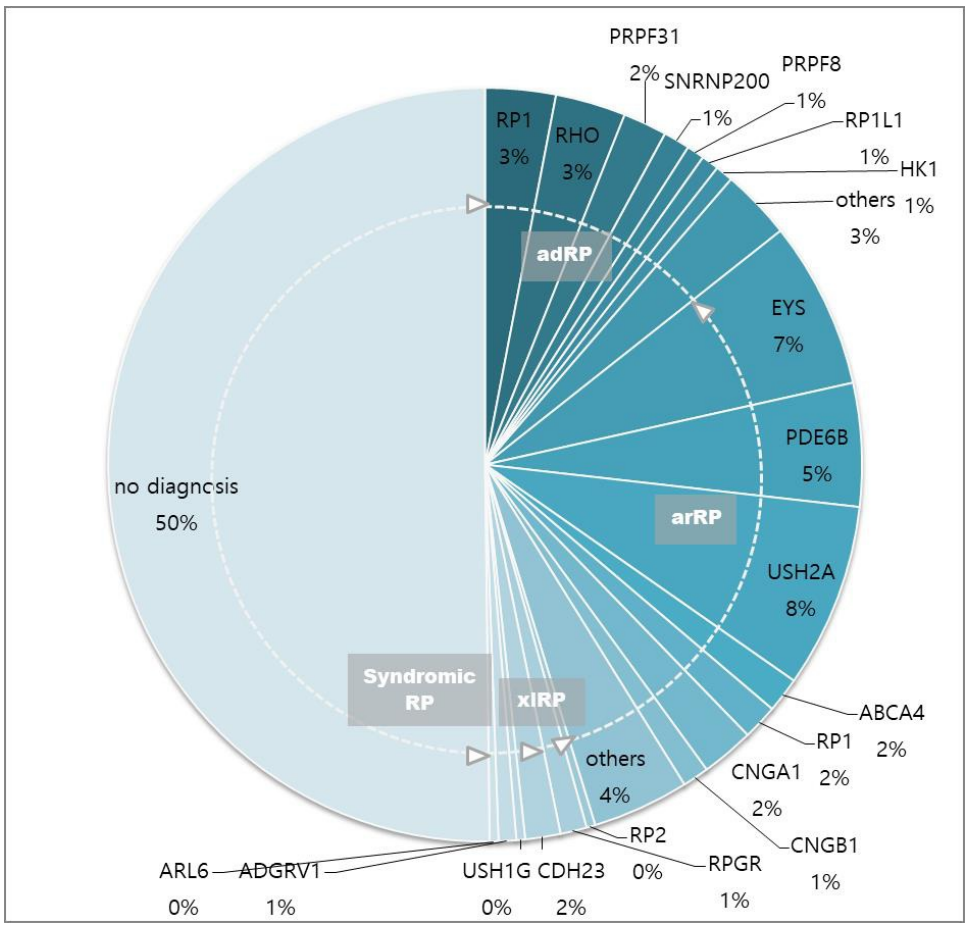

Figure 2. Mutational spectrum in 265 Korean patients with retinitis pigmentosa confirmed by both next-generation sequencing and whole exome sequencing.

Correlation between Visual Function and Macular Morphological Characteristics Evaluated by SD-OCT in X-Linked Retinoschisis

- Honghua Yu, MD, PhD
- Qiaowei Wu, MD
- Baoyi Liu

OBJECTIVE If any correlation between visual acuity and morphological characteristics revealed by spectral-domain optical coherence tomography in patients with X-linked retinoschisis.

PURPOSE The aim of the study was to use the spectral-domain optical coherence tomography (SD-OCT) to reveal morphological changes in the macula and to evaluate the correlation between visual acuity and morphological characteristics in patients with X-linked retinoschisis (XLRS)

METHODS Seventy-two eyes of 39 patients with XLRS were included. The foveal thickness (FT), central subfield thickness (CST), macular volume (MV), the area of macular schisis cavity (AMS), ellipsoid zone (EZ) and interdigitation zone (IZ) were measured by SD-OCT. Correlations between these structural properties and best-corrected visual acuity (BCVA) were analyzed.

RESULTS The SD-OCT images showed that macular schisis cavities were present in all 72 eyes (100%) and peripheral retinoschisis were present in 34 eyes (47.2%). Macular schisis cavities were seen in multiple retinal layers and predominantly in the inner nuclear layer (100%). The logMAR BCVA was significantly correlated with CST ($r = 0.717$, $P < 0.001$) and AMS ($r = 0.475$, $P < 0.001$) rather than with FT or MV. The photoreceptor defects were correlated with logMAR BCVA (EZ, $r = 0.563$, $P < 0.001$; IZ, $r = 0.391$, $P = 0.001$).

CONCLUSION SD-OCT revealed various retinal splitting changes in patients with XLRS.

The macular schisis was most frequently seen in the inner nuclear layer. The CST, AMS and photoreceptor defects might be indicators for evaluating the macular and the visual function.

HUMAN RESEARCH Yes: Approved by institutional review board

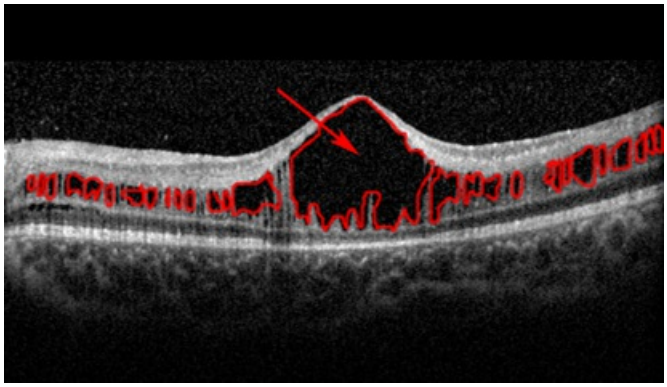

Fig. 1. The measurement of are of macular schisis cavities (AMS). The macular schisis cavities were marked by red lines and were measured by ImageJ software.

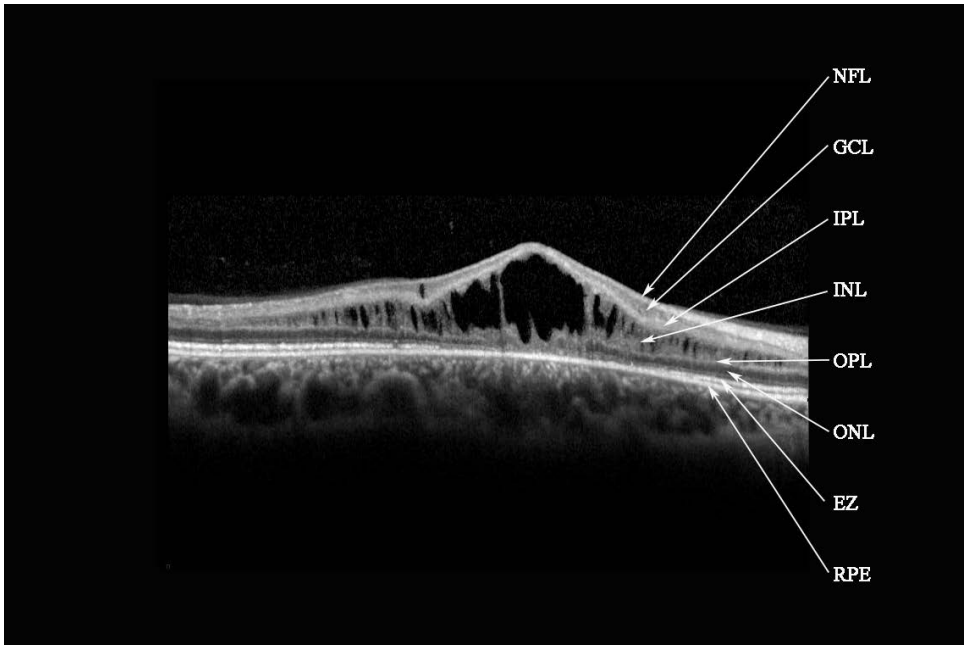

Fig. 2. Spectral-domain optical coherence tomography image reveals macular schisis cavities in the inner nuclear layer (INL), OPL (outer plexiform layer) and outer nuclear layer (ONL). Small cystic cavities were seen in the ganglion cell layer (GCL). NFL = nerve fiber layer; IPL = inner plexiform layer; EZ = ellipsoid zone; RPE = retinal pigment epithelium.

AAV-RPGR Gene Therapy for RPGR-Associated X-Linked Retinitis Pigmentosa: 6-month Results From a Phase 1/2 Clinical Trial

- Michel Michaelides, BSc, MB BS, MD(Res), FRCOphth, FACS
- Cagri G Besirli, MD, PhD
- Kamron Khan
- Yesa Yang
- Sui Chien Wong, MBBS,FRCSEd(ophth),MRCOphth
- J-S Sahel, MD
- Mahmood Shah
- James Tee
- Neruban Kumaran, PhD FRCOphth
- Tassos Georgiadis
- Stuart Naylor
- Peggy Wong
- Penny Fleck, MT, MBA
- Alexander J Smith, PhD
- Robin Ali, Ph.D.
- Alexandria Forbes
- James Bainbridge

OBJECTIVE To investigate the safety and efficacy of a gene therapy for X-linked retinitis pigmentosa (XLRP) associated with disease-causing sequence variants in Retinitis Pigmentosa GTPase Regulator (RPGR).

PURPOSE RPGR-associated XLRP is among the most severe forms of retinitis pigmentosa, the most prevalent inherited retinal dystrophy. MGT009 is a multi-center open-label Phase 1/2 trial (NCT03252847) of an AAV-RPGR gene therapy consisting of 3 phases: dose-escalation, dose-confirmation, and dose-expansion.

METHODS In dose-escalation, adults were given ≤1 mL subretinal injection of low, intermediate, or high dose AAV-RPGR; the better-seeing untreated eye was a control. Max acceptable dose was confirmed in 3 children. In dose-expansion, adults were randomized to low dose, intermediate dose, or deferred treatment. Central retina was targeted with foveal detachment; multiple retinotomies allowed full retinal coverage. The primary endpoint was safety. Function was assessed at baseline, 3, 6, 9 and 12 mo with Octopus 900 full-field static perimetry and mesopic fundus-guided microperimetry (MM); mean retinal sensitivity, visual field modeling and analysis (VFMA), and point-by-point comparisons were examined.

RESULTS Six-month outcomes of the dose-escalation phase are reported. AAV-RPGR was generally well-tolerated. In low (n=3) and intermediate (n=4) dose cohorts, 5/7 subjects demonstrated improvement or stability in retinal sensitivity in the treated eye (full-field static perimetry and MM). Efficacy signals were observed at first post-treatment assessment at 3 mo, with improvements sustained or increased at 6 mo. VFMA-derived improvement in the central 30-degree hill-of-vision (V30) was observed in the treated eyes vs baseline (0.67 dB-sr [90% CI: 0.13, 1.20]), while V30 in the untreated eye did not improve vs baseline (−0.39 dB-sr [90% CI: −0.76, −0.02]), with significant differences

observed between treated and untreated eyes (1.06 dB-sr; P <0.05). Improvement in central retinal sensitivity was also evidenced by changes in MS and point-by-point comparisons over the same period. Similar improvements were observed with MM. In the high dose cohort, inflammation was evident in 2/3 subjects.

CONCLUSION In this trial, low and intermediate dose cohorts achieved clinically meaningful improvements in retinal sensitivity evident across multiple metrics and modalities. Given the robust safety and efficacy signals observed, these doses are being further explored with analyses at additional data time-points in the ongoing randomized, controlled dose-expansion phase of the study.

HUMAN RESEARCH Yes: Approved by institutional review board