Subthreshold Diode Micropulse Laser (SDM) as Retinal Protective Therapy for Non-Age Related Retinal Degenerations

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OBJECTIVE To show that subthreshold diode micropulse laser (SDM) retinal protective therapy (RPT) can improve both retinal and visual function in non-age related chronic progressive retinopathies (CPRs).

PURPOSE To examine the effect of SDM PRT on retinal function measured by pattern electroretinography (PERG) and visual function measured by Omnifield resolution perimetry (ORP) in non-age related CPRs.

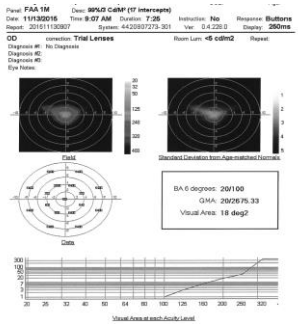
METHODS The records of all patients (pts) undergoing SDM RPT in a vitreoretinal subspecialty practice were reviewed. Inclusion criteria included the presence of a non-age related (and non diabetic) CPR evaluated before and after RPT by PERG. Exclusionary criteria included other obfuscating ocular disease; poor quality or unreliable PERG testing; recent ocular surgery, and loss to follow up. Among latter pts, ORP was performed in addition to PERG.

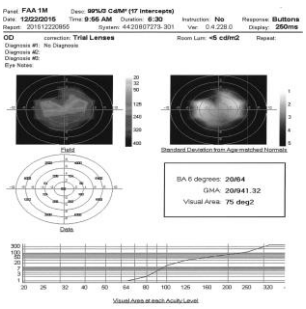
RESULTS All eyes undergoing RPT for CRPs were eligible study. These included 21 eyes of 12 pts; 5 male and 7 female, aged 27-79 (avg. 58) years. Diagnoses included rod-cone degeneration / retinitis pigmentosa (7 pts, 13 eyes), cone-rod degeneration (2pts, 3 eyes), Stargardt's disease (2 pts, 3 eyes), and vitamin A deficiency retinopathy (1 pt, 2 eyes). Retinal function by PERG was improved in 19/21 eyes, with significant

improvements in the 24° Mag(D)/Mag(uv) ratio (P=0.0009) and the 24° Mag(D) (P=0.01). ORP improved in 7/7 pts and 11/13 eyes tested. One eye with Stargardt's disease was unimproved by PERG and ORP. LogMAR visual acuities were unchanged. There were no adverse treatment effects.

CONCLUSION As predicted by the Reset to Default Theory of retinal laser action, SDM RPT significantly improved both retinal and visual function in non-age related CPRs without adverse treatment effects. Treatment responses indicate a significant capacity for rescue of dysfunctional retina in CPRs, suggesting early treatment with SDM RPT may reverse and/or slow disease progression and reduce the risk of vision loss.

TAKE HOME MESSAGE Reset to Default theory describes the mechanism of retinal laser treatment, and predicted the improvements observed in non-age related CPRs produced by SDM RPT.





HUMAN RESEARCH This study involves human research.
IRB Approval Status: Exempt from approval

Visual Acuity Sensitivity/Subgroup Analyses From a Phase 3 Trial of AAV2-hRPE65v2 (*SPK-RPE65*) in *RPE65* Mutation-Associated Inherited Retinal Dystrophy

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OBJECTIVE We report the visual acuity results at Year 1 from the first completed Phase 3 gene therapy trial.

PURPOSE To evaluate visual acuity (VA) outcomes, which are primarily cone-mediated, at Year 1 from the AAV2-hRPE65v2 (*SPK-RPE65*) gene therapy study (NCT00999609) to treat *RPE65* mutation-associated disease, which is principally a rod-mediated degeneration.

METHODS Thirty-one subjects with disease-causing biallelic *RPE65* mutations were randomized 2:1 to intervention or control (intent-to-treat, ITT); 29 then entered the intervention or control (observation) phase through Year 1 study assessments. Interventions subjects received subretinal injections of AAV2-hRPE65v2 sequentially to each eye within 18 days, with the injection site centered above the macula. To minimize amblyopia, the poorer-seeing eye was injected first. Best-corrected visual acuities were measured using an ETDRS chart and converted to a LogMAR scale. For acuities below the range of ETDRS at 0.5m, Freiburg Visual Acuity Test (FrACT) values were used (Lange et al., 2009).

RESULTS Analyzed on a mITT basis and applying FrACT values for low acuities, intervention subjects showed a 9 letter improvement vs. a 1.5 letter improvement in controls across both eyes (p=0.047). The assigned first eye was improved by 10.5 letters vs. 2 letters for un-injected control subjects (p= 0.059). Six of 20 first injected eyes had 15 or more letters (≥ 0.3 LogMAR) gained vs. none of the control subject eyes; one intervention subject, who presented with a cataract at Year 1 had a loss of 15 or more letters at this visit. Assigned second eyes improved 7.5 letters in intervention subjects vs. 1 letter in control subjects (p=0.081). Four of 20 second injected eyes had 15 or more letter improvement vs. none of the control subject eyes. When 3 intervention subjects that developed post-intervention cataracts are excluded, the average VA improvement was 10.6 letters vs. 1.5 for controls across both eyes (p=0.007).

CONCLUSION Sensitivity visual acuity analyses showed trends toward improvement in individual eyes, and statistically significant improvement across both eyes, following bilateral administration of AAV2-hRPE65v2 in this rod-dominated disorder. For subjects that did not develop post-intervention cataracts, average change in visual acuity across both eyes was highly statistically significantly improved.

TAKE HOME MESSAGE Gene augmentation therapy for RPE65 mutation-associated inherited retinal diseases using AAV-hRPE65v2 may result in improvements in visual acuity unless cataracts develop after intervention.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

North Carolina Macular Dystrophy (MCDR1): Mutations Found Affecting PRDM13

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OBJECTIVE To identify mutations causing North Carolina macular dystrophy (NCMD, MCDR1).

PURPOSE We originally reported four mutations affecting PRDM13 in eleven families causing North Carolina Macular Dystrophy. An international cohort of additional 20 families were sequenced and analyzed reporting mutations causing North Carolina macular dystrophy (NCMD, MCDR1).

METHODS We intially performed targeted Nex Gen sequencing of the MCDR1 region (870kb) in 8 affected individuals from 3 families representing 3 different haplotypes affected with chromosome 6 linked NCMD (MCDR1). In addition to our original 11 MCDR1 families recently published (141 total subjects), we now have an additional

cohort of 23 families with the NCMD phenotype available for study (total of 367 subjects, 32 families).

RESULTS We initially found 14 rare variants spanning 870kb of the disease-causing allele. One of these variants (V1, ch6:1000400906) was absent from all published databases and all 261 controls, but was found in a total of 13 NCMD kindreds. This variant lies in a DNase 1 hypersensitivity site (DHS) upstream of both the PRDM13 and CCNC genes. Sanger sequencing of 1 kb centered on V1 was performed in the remaining NCMD probands, and 2 additional novel single nucleotide variants (V2, ch6:10000987, in 6 families and V3, ch6:100041040 in 1 family) were identified in the DHS within 134 bp of the location of V1. A complete duplication of the PRDM13 gene was also discovered in a single family (V4). The 4 mutations V1 to V4 segregated perfectly in the 118 affected and 33 unaffected members of the 21 NCMD families.

CONCLUSION We identified 4 rare mutations in a non-coding region, each capable of arresting human macular development by causing over expression of PRDM13. Additional families with the NCMD phenotype continue to support that these mutations are causative of MCDR1 / NCMD.

TAKE HOME MESSAGE The additional families with North Carolina Macular Dystrophy phenotype provide additional evidence confirming the mutations in PRDM13 causing North Carolina Macular Dystrophy.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board