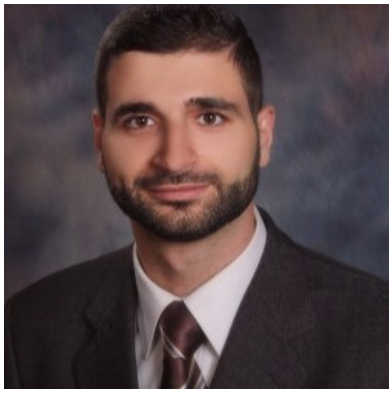
7/31/2023 12:00 am

Hereditary Retinal Disease & Genetics Symposium

Epidemiology of Inherited Retinal Diseases in the United States: IRIS Registry (Intelligent Research In Sight) Analysis



- Ahmad Al-Moujahed, MD, PhD, MPH
- Md Enamul Haque
- Rachel Huckfeldt, MD, PhD
- Suzann Pershing, MD

Objective: What is the epidmiology of inhereted retinal diseases in the United States?
Purpose: Inherited retinal diseases (IRDs) are visually devastating diseases. Improving our knowledge of the epidemiology of these diseases and their comorbid conditions will improve patient care and help us design better studies in the field of IRDs. The aim of this study is to evaluate the incident cases, characteristics, and comorbid conditions of IRDs in the United States.

Methods: Retrospective cohort analysis of patients with a new IRD diagnosis in the American Academy of Ophthalmology IRIS® Registry (Intelligent Research In Sight), 2013-2019. IRDs were broadly classified by anatomic location (neurosensory retina/RPE or choroid). Color blindness was considered separately. Based on the availability of disease-specific ICD codes, we focused on three diseases: retinitis pigmentosa (RP), choroideremia, and color blindness.
Results: Overall, 227,011 IRIS Registry patients (41% male, 59% female) carried a new IRD diagnosis. Diseases of the neurosensory retina and RPE were most common (85%), followed by choroidal diseases (13%), and color blindness (2%). 38,179 patients had RP (15% of all patients with IRDs; 20% of patients with a neurosensory retina or RPE disease), whereas 540 patients had choroideremia (0.2% of all patients with IRDs; 2% of patients with a choroidal disease) and 4,563 had color blindness. Most patients with RP and choroideremia (35% and 32%, respectively) were 45-64 years old, whereas most patients with color blindness (33%) were 0-17 years old.
Best-corrected visual acuity (BCVA) at diagnosis was worst for patients with choroideremia (mean 0.48 logMAR, standard deviation (SD) = 0.76), followed by RP patients (mean 0.40 logMAR, SD = 0.66) and patients with color blindness (mean 0.12 logMAR, SD = 0.21). Patients with choroideremia were more likely to be legally blind compared to those with RP or color blindness (5% vs 2% and 0.004%, respectively).
Cataract diagnosis and surgery were more frequently seen after IRD diagnosis in patients with RP and choroideremia (46% and 45%, respectively) than in color blindness patients (29%), as was rhegmatogenous retinal detachment (RRD) diagnosis or repair (4% RP patients and 6% of choroideremia patients, versus 2% of those with color blindness). Patients with RP and choroideremia were also more likely to have cystoid macula edema (CME) (13% and 10%) and choroidal neovascularization (CNV) (4% and 6%) compared to patients with color blindness (3% CME and 1% CNV).
Conclusion: Although rare, IRDs and their comorbid conditions can be evaluated using the IRIS Registry due to its large scale. IRD patients can develop treatable ocular conditions that may further affect their vision.

IRB APPROVAL No - no IRB

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Hereditary Retinal Disease & Genetics Symposium

North Carolina Macular Dystrophy (NCMD/MCDR1): Analysis of Our Entire Database, a Model Disease of Noncoding Mutations

- Kent Small, MD

Objective: Do our initial molecular findings of NCMD continue to be substantiated today?
Purpose: We reported the first 5 mutations in 12 NCMD families with 141 subjects. The purpose of this study is to clinically and molecularly study our entire NCMD database to determine if our initial findings continue to be substantiated.
Methods: Ophthalmic examinations and whole genome sequencing (WGS) and/or targeted DNA Sanger sequencing was performed on our entire dataset of 55 families with 384 subjects. Junction PCR and Sanger sequencing was used to confirm point mutations and characterize duplications involving the MCDR1/MCDR3/PRDM13 locus.
Results: Of the total 384 subjects evaluated to date, 272 were found to be affected having DNA sequence changes consistent with MCDR1 on chromosome 6 or MCDR3 on chromosome 5. Unaffected family member sequences was 117 subjects. In addition to our 12 initial families, we report the findings of an additional 43 families with 78 subjects affected and 41 unaffected. Eight of these new families, 35 subjects, were found to have the original “V1” Chr6:99593030G>T mutation, in a non-coding region of the DNASE1 site upstream of PRDM13. Fourteen families, 50 subjects, had the “V2” mutation Chr6:99593111G>C in the same DNASE1 site. One Asian family with 2 subjects had our previously reported Asian “V3” Chr6:99593164C>T mutation in the same DNASE1 site. Two new single nucleotide variants (SNVs) have recently been reported by us from our dataset, Ch6:99599064A>G in four members of one Czech family and Chr6:99959303G>C in four members of a Mexican family. A new tandem duplication Chr6:99560265-99616492 involving the same DNASE1 site, was recently reported by us in a Turkish family. Two novel non-coding point mutations at chr6:g.99598914T>C and chr6:g.99598926G>A (hg38) in the non-coding region of the DNase I site were found in two Korean families. A previously unreported geographic origin for this phenotype.
Conclusion: North Carolina Macular Dystrophy (NCMD) is more prevalent than typically thought with a worldwide distribution making the name of this disease a gross misnomer. Continued identification of subjects and families and their mutations supports our initial discovery of mutations. Our group has found 10 of 15 total NCMD mutations. All of the mutations (SNVs and duplications) appear to involve DNASE1 sites in non-coding regions. This suggests that this DNASE1 site is a mutational hot spot and confirms our original findings that it is critical in regulating PRDM13.

IRB APPROVAL Yes

7/31/2023

MCO-010 Optogenetic Therapy for Severe Vision Loss in Stargardt Disease: 6-Month Outcomes From the Phase 2 STARLIGHT Trial
MCO-010 Optogenetic Therapy for Severe Vision Loss in Stargardt Disease: 6-Month Outcomes From the Phase 2 STARLIGHT Trial

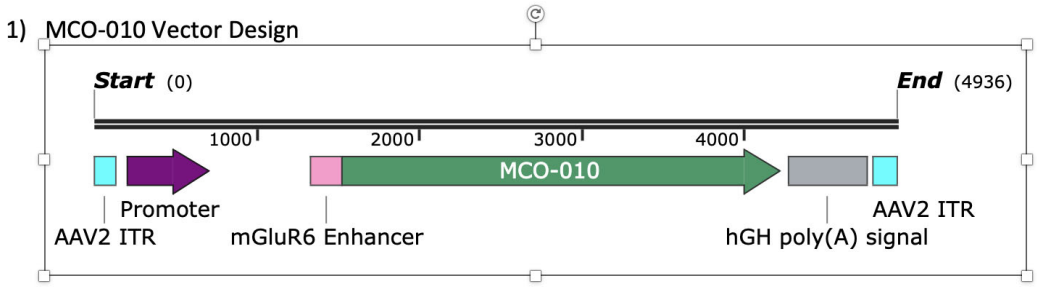
- Allen Ho, MD FASRS

Objective: What is the safety and efficacy of MCO-010 Optogenetic therapy for Stargardt's disease in a Phase 2 clinical trial?
Purpose: Optogenetic therapy holds promise as a potential mutation agnostic therapy for a variety of retinal degenerations. MCO-010 is an intravitreal, adeno-associated Virus (AAV2)-delivered optogenetic therapy designed to treat severe vision loss from outer retinal degenerative disease. Stargardt disease is a rare, inherited condition with significant unmet need, characterized by progressive photoreceptor and outer retinal degeneration eventually leading to profound vision loss. STARLIGHT (NCT05417126) is a Phase 2 open label multi-center clinical study to evaluate the safety and effects of a single dose level of MCO-010 in subjects with Stargardt disease.

Methods: Prospectively, participants in the STARLIGHT trial were required to have a documented clinical diagnosis of Stargardt disease (classic fleck phenotype and/or well-demarcated sub-foveal area of significantly reduced autofluorescence as imaged by FAF), or genetic diagnosis with pathogenic variants in ABCA4, ELOVL4, or PROM1. All subjects received a single intravitreal injection of 1.2E11 gc/eye MCO-010 in the study eye at baseline. Ocular and systemic safety, as well as multiple vision function tests, including Best-Corrected Visual Acuity (BCVA) using ETDRS charts at 50 cm with and without wearable magnifier, Octopus Visual Field Perimentry, Multi-Luminance Y-Mobility Test (MLYMT) and Multi-Luminance Shape Discrimination Test (MLSDT) were assessed. Rasch-validated Michigan Retinal Degeneration Questionnaire (MRDQ) was used for evaluating patient reported outcome.
Results: 6 participants, 4 males and 2 females, with severe vision loss due to Stargardt disease were enrolled between June and September 2022. Mean age was 49 years (range 32-71). At baseline mean study eye BCVA letter score was 23 (range 9-35). Patients with predominantly macular atrophy experienced clinically meaningful improvements in BCVA. After MCO-010 treatment, the patients exhibited ~ 3 dB gain in mean sensitivity measured by Visual Field Perimetry. High baseline MLYMT and MLSDT performance was maintained throughout study. MCO-010 treated Stargardt patients reported significant improvements in key MRDQ domain scores: Reading, Color & Contrast. MCO-010 was well-tolerated with no serious adverse event reported.

Conclusion: STARLIGHT is the first clinical study of optogenetic therapy for severe vision loss due to Stargardt disease. Optogenetic thereapy is a promising approach and outcomes from STARLIGHT will help inform the future clinical development of MCO-010 therapy for vision restoration in Stargardt disease and other retinal degenerative conditions.

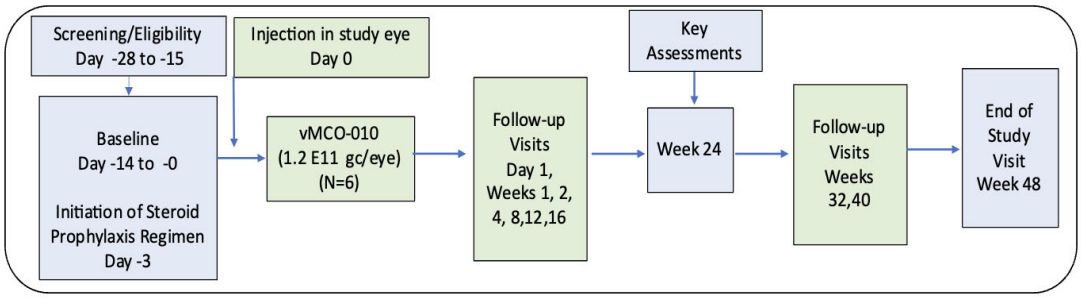
IRB APPROVAL Yes



Schematic of the MCO-010 vector genome. The cloned nucleic acid sequences coding for the multi-characteristic opsin (MCO) including mCherry reporter and stabilizer are followed by the human growth hormone (hGH) polyadenylation signal for mRNA transcript stability. Expression from the cassette is driven by a promoter and mGluR6 enhancer specific to ON bipolar cells of retina. ITR: Inverted terminal repeats.

Schematic of the MCO-010 vector genome

2) STARLIGHT Phase 2 Study Design Schema



STARLIGHT Phase 2 Study Design Schema

7/31/2023

Eighteen-Month Results From the Phase 1b/2 Study of Tinlarebant in Adolescent Subjects with Stargardt Disease
Eighteen-Month Results from the Phase 1b/2 Study of Tinlarebant in Adolescent Subjects with Stargardt Disease

- Quan Nguyen, MD, MSc, FARVO, FASRS
- Michael Michaelides, MD
- Webber Liao, PhD
- Nathan Mata, PhD
- John Grigg, MBBS, MD

Objective: To evaluate the safety, tolerability, and efficacy of tinlarebant in adolescent subjects with Stargardt Disease (STGD1)
Purpose: To present for the first time the 18-month results from the Phase 1b/2 study of adolescent STGD1 patients treated with Tinlarebant, an orally available retinal binding protein 4 (RBP4) antagonist.

Methods: Safety and efficacy data for subjects aged 12 to 18 years receiving daily doses (5 mg) over 2 years are evaluated and compared to natural history study. Visual function outcomes including fundus autofluorescence (FAF), spectral-domain optical coherence tomography (SD-OCT) and best-corrected visual acuity (BCVA) are evaluated for all subjects in this study.

Results: At Month 18, FAF data showed a slower annual DDAF growth rate of 0.22 mm^2/year (OU) compared to natural history studies. Furthermore, 7 out of 12 subjects have maintained no DDAF lesion after 18 months of treatment. SD-OCT data showed stabilization or improvement of EZ loss width in 3 out of 6 subjects with evaluable images, including 2 subjects who have showed consistent improvement throughout the Phase 2 portion of the study. Assessment of the retinal thickness also showed less retinal thinning compared to the natural history study. In addition, 10 of 12 subjects maintained BCVA over the 18-month period. Tinlarebant is well tolerated and safe in all subjects after 18 months of treatment. All AEs emergent during treatment period were graded mild. All treatment-related AEs were ocular and considered to be related to the mechanism of action of Tinlarebant.

Conclusion: Tinlarebant is safe and well tolerated as a therapy in this first ever worldwide interventional study for STGD1 adolescents. After 18 months of treatment, there are trends of slower expansion of atrophic lesions and reduced retinal thinning. Maintenance of vision in the majority of subjects is also found.

IRB APPROVAL Yes

7/31/2023 12:00 am

Hereditary Retinal Disease & Genetics Symposium

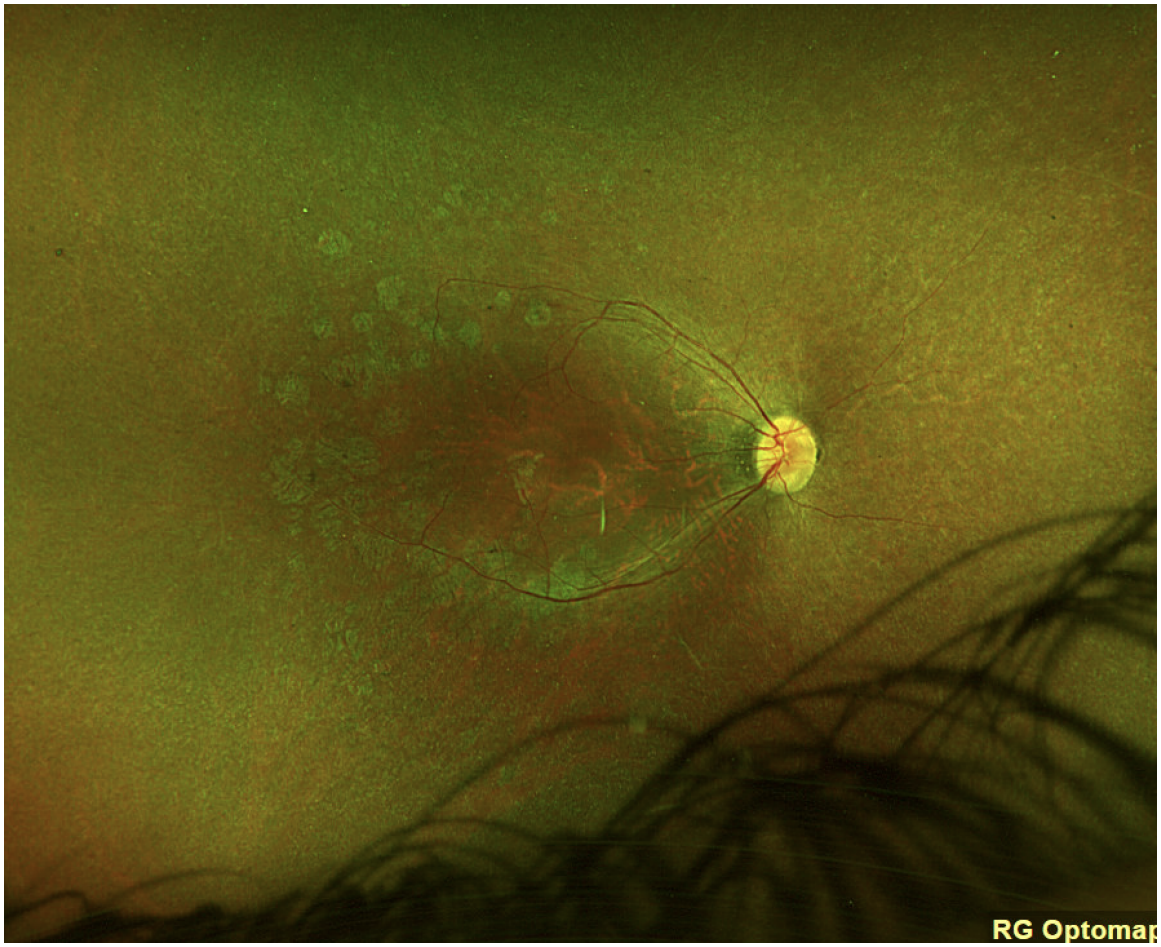
Complications of Transvitreal Subretinal Injections for Gene Therapy Vectors in Inherited Retinal Diseases

- Chloe Khoo, MD
- Robert Sisk, MD, FACS, FASRS

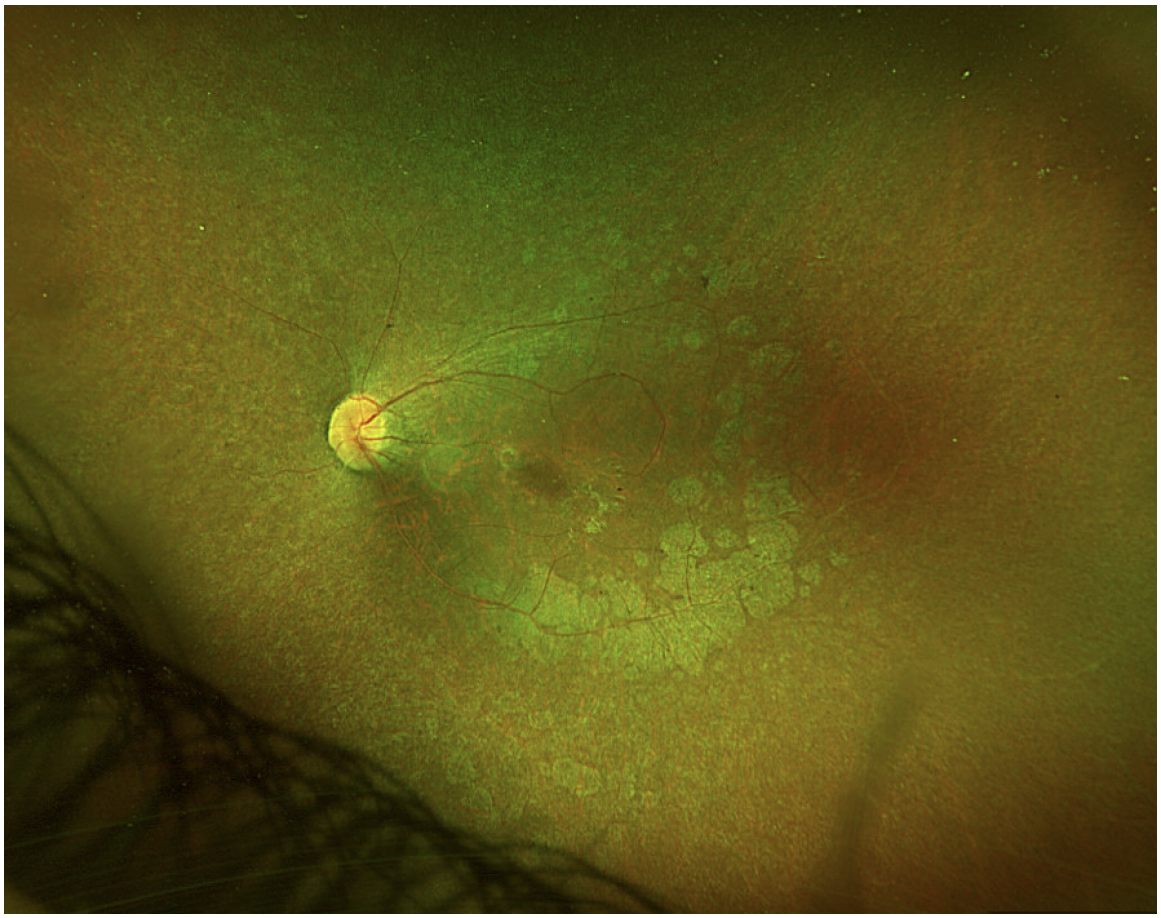
Objective: To describe the complications of transvitreal subretinal injections in gene augmentation therapy for inherited retinal diseases (IRD).
Purpose: Transvitreal subretinal injection (TSI) during vitrectomy is the preferred approach for gene augmentation therapy. Complications are common and some are unique to specific IRDs. We describe the variety of complications, their attribution, management, and prevention.
Methods: Retrospective review of all TSI gene therapy procedures performed by a single surgeon between September 2018 and April 2022 for various IRDs. Main measures include complications associated with the surgical procedure, the vector, and the steroid regimen.
Results: 70 eyes in 46 patients (18 females, 39.1%) with IRD underwent transvitreal subretinal injection of AAV2 vectors for ocular gene transfer of *RPE65* (44 eyes of 23 patients), *REP1* (7 eyes of 4 patients), *RPGR* (5 eyes of 5 patients), *CNGA3*(5 eyes of 5 patients), and *CNGB3* (9 eyes of 9 patients). Mean age was 22 years (median 21, range 2-56) with a mean follow up of 577 days (median 530, range 7-968). Of the 70 eyes, 22 eyes (31.4%) had complications related to the surgical procedure itself which include retinal tears (n=8), foveal schisis (n=4), lamellar macular hole (n=2), RPE changes (n=7), RPE atrophy from injection cannula touchdown (n=4), choroidal neovascularization (n=1) after inadvertent suprachoroidal injection. Complications related to the vector were seen in 18 eyes (25.7%) and include uveitis beyond the immediate postsurgical period (n=7) and chorioretinal (CR) atrophy (n=11), which represented 35.5% of *RPE65* eyes with at least 6 months follow-up and correlated with longer duration of follow-up (p=0.0015). Steroid-induced intraocular pressure elevation was observed in 23 eyes (32.9%). Delayed visual recovery, defined as failure to reach baseline visual acuity at one-month postoperatively was observed in 22 eyes (32.9%) associated with preoperative loss of foveal ellipsoid zone (EZ) on SDOCT (p=0.0018). Baseline visual acuity (VA) was predictive of 6 months post-operative VA (p<0.001). Most complications (97.1%) were mild to moderate in severity, treatable, and did not impact the final visual acuity outcome.

Conclusion: Complications are common with the TSI technique for gene augmentation therapy for IRDs. Rate of CR atrophy observed among *RPE65* eyes increased with duration of follow-up. However, most complications did not impact final VA. Intact retinal anatomy, especially preoperative foveal EZ, provided more rapid VA recovery and tolerance against visual deficits from complications.

IRB APPROVAL Yes



Chorioretinal atrophy OD 3 years after voretigene neparvovec



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