8:00 AM

Year 4 Results For a Phase 1 Trial of Voretigene Neparvovec in Biallelic *RPE65*-Mediated Inherited Retinal Disease

- Albert M. Maguire, MD

OBJECTIVE Assess maintenance of functional vision/visual function improvements 4 years after voretigene neparvovec (VN) administration in subjects with biallelic *RPE65*-mediated inherited retinal disease (IRD).

PURPOSE A follow-on phase 1 trial of VN administered to the second eye of subjects with biallelic *RPE65*-mediated IRD showed marked improvement in subjects' ability to navigate in varying light levels, as measured by a multi-luminance mobility test (MLMT), and full-field light sensitivity threshold (FST) testing. Here, we present 4-year results from ongoing evaluation of this cohort.

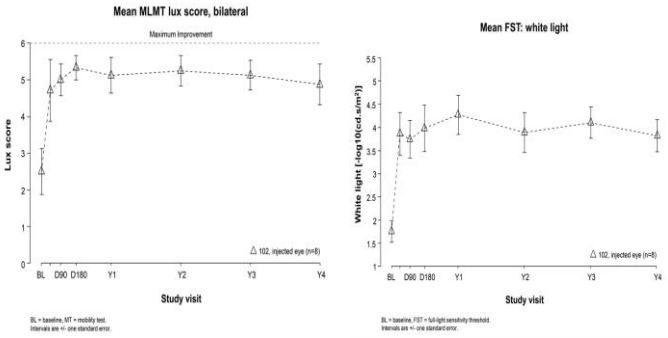
METHODS 0.3 mL of VN was injected subretinally into the contralateral, previously uninjected eyes of 11 subjects with biallelic *RPE*65 mutations, 1.7 to 4.6 years after initial unilateral injection. Subjects were tested for accuracy and speed on MLMT at standardized illumination levels ranging from 1 to 400 lux. The lowest level that subjects could pass MLMT was established at baseline and follow-up visits to determine change in lux score. An additional endpoint, FST, measured sensitivity to white light over a range greater than 5 log units. Four-year data are presented for the 8 of 11 subjects in this follow-on phase 1 study who would have been eligible for a subsequent phase 3 study.

RESULTS Mean MLMT lux score change remained stable at 2.4 ± 0.46 at 4 years compared with 2.6 ± 0.56 at 1 year (Figure 1). Average improvement in FST was also maintained, with 4-year white light sensitivity measures of -3.82 ± 0.98

log10(candela.m/sec²) compared with -4.27 ± 1.21 log10(candela.m/sec²) at 1 year (Figure 2). Compared with baseline, this represents a greater than 100-fold average improvement in FST, which was maintained over 4 years. No serious adverse events associated with VN or deleterious immune responses have been observed.

CONCLUSION Mean improvements in functional vision, measured by MLMT, and visual function, measured by FST, were maintained through 4 years in a follow-on phase 1 clinical trial of VN for *RPE65*-mediated IRD. These findings add to the clinical evidence supporting the potential long-term effect of bilateral treatment with VN.

TAKE HOME MESSAGE Functional vision/visual function improvements were maintained 4 years after voretigene neparvovec (VN) administration in subjects with biallelic *RPE65*-mediated inherited retinal disease (IRD).



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

8:08 AM

Phase 2 Tolerability and Effects of ALK-001 in Stargardt Disease (“TEASE” Trial): An Update

- Christine Kay, MD
- Jing Zhang, MD
- Leonide Saad, PhD

OBJECTIVE To evaluate safety, tolerability and pharmacokinetics of daily oral ALK-001 in patients over 12 years old with ABCA4-related Stargardt disease, and determine effects on growth rate of atrophic lesions

PURPOSE Disease-causing variants in the *ABCA4* gene cause improper transport of vitamin A in the retina and rapid formation of dimers of vitamin A, such as A2E, and downstream byproducts, together thought to be responsible for vision loss in Stargardt (STGD1). No treatment currently exists. Here we present the ongoing Phase 2 "TEASE" trial study design, as well as baseline, safety and pharmacokinetic data.

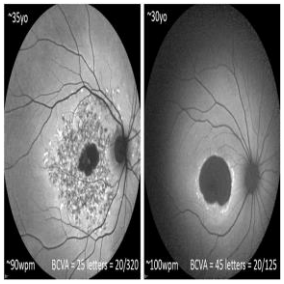
METHODS ALK-001 (deuterated vitamin A) is delivered once-a-day as a pill. When ALK-001 replaces the majority of vitamin A, it slows vitamin A dimerization by about 4-5 fold. TEASE is a prospective Phase 2 double-masked placebo-controlled study, enrolling up to 50 subjects with STGD1, aged 12 years or older, and with a well-delineated area of atrophy in at least one eye. Subjects can have any visual acuity to enroll, and are randomized 3:2 to ALK-001 or placebo during the first year of treatment. After a year, one-half of subjects receiving placebo cross over to ALK-001 in a masked fashion.

Outcome measures include best corrected visual acuity (BCVA), reading speed, and size of atrophic lesion.

RESULTS 44 of the 50 subjects (33 White; 22 Female) have been enrolled at 7 clinical sites in the USA. Median age was 46 years (range, 18-60) and disease duration 13 years (2-57). For subjects with 1 or 2+ *ABCA4* mutations, the median age of onset of symptoms was 44 or 30 years, respectively. The median BCVA at baseline was 60 letters (8-91) or 20/125. The median reading speed was 104 wpm (2-199) or about 44% of normal speed; each decrease in BCVA of 20 letters in the best eye was associated with a decrease of about 25 wpm in reading speed. Atrophic lesions were bilateral in 75% of cases with a 5.1 mm^2 (0.25-31.6) median area. As of January 2017, the median treatment duration was ~12 months. Plasma pharmacokinetic analyses indicate that over 90% of vitamin A was replaced with deuterated vitamin A. There have been no reports of night blindness or impaired dark adaptation, indicating that deuterated vitamin A does not slow down the visual cycle.

CONCLUSION Preventing vitamin A dimerization may slow the progression of retinal degenerations such as STGD1 and AMD. Preserving the visual cycle is however critical to prevent long term retinal complications. ALK-001 is the first molecule to slow vitamin A dimerization without interfering with the visual cycle. The TEASE Phase 2 study is currently the largest effort to slow or prevent progression of STGD1.

TAKE HOME MESSAGE Replacing vitamin A with one that will not dimerize, ALK-001 (deuterated vitamin A), may result in a treatment of Stargardt disease, a juvenile cause of macular degeneration. Phase 2 study is ongoing.



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

8:16 AM

Reactivation of Dormant Cones in Retinitis Pigmentosa (RP)

- Henry J. Kaplan, MD

OBJECTIVE The ability of rod progenitor cell transplants to rescue dormant cones and identification of the mechanism of this rescue effect.

PURPOSE RP is a disease caused by genetic mutations in rods that result in their dysfunction and death. However, it is the subsequent loss of cone photoreceptor function (i.e. the development of dormant cones) that is responsible for loss of functional vision. We studied the ability of rod progenitor cell transplants to rescue dormant cones and identified the mechanism of this rescue effect.

METHODS The pig model of P23H retinopathy has a visual streak (i.e. an area of cone dominance) that is analogous to the macula and allows the study of cone photoreceptors function and structure. Porcine embryonic day 65 (E65) normal (i.e. wild-type) rod progenitor cells or rod-differentiated induced pluripotent stem cells (iPSCs) were transplanted into the subretinal space in P23H retinopathy at P60 – a time when there are no rod photoreceptors and there is total loss of cone outer segments (OS). Morphologic studies (light microscopy, immunohistology and electron microscopy) and electrophysiology (multifocal ERG [mfERG]) were performed at 1-3 months post transplantation.

RESULTS Both E65 rod progenitor cells and rod-differentiated iPSCs when transplanted at P60, when cone OS are lost, resulted in the regrowth of opsin^{+} cone OS for a radius of 1000μm from the transplant site beneath the visual streak. Additionally, the photopic mfERG was increased in regions surrounding the transplant site correlating with endogenous cone OS restoration. No effect was seen with the sham transplant. Since we have evidence that glucose becomes sequestered in the RPE and is not delivered to photoreceptors in the P23H retina, we injected glucose at a concentration of 280 mM in 50μl beneath the visual streak in the P23H retina at a time when rods are lost and cones retain inner segments but no OS; media was injected in the contralateral eye. After three days we found that opsin^{+} cone OS were restored in a 1500μm radius from the site of glucose injection but not in the eye with subretinal media.

CONCLUSION Transplanted rod precursors results in endogenous cone OS synthesis and the return of dormant cone electrophysiologic function. Rod photoreceptor loss limits cone access to glucose which becomes trapped in the RPE. Furthermore, subretinal injection of glucose alone reactivates cone OS synthesis and induces enzymes in cone photoreceptors associated with the aerobic metabolism of glucose.

TAKE HOME MESSAGE Rod photoreceptor loss limits cone access to glucose in RP which becomes trapped in the RPE. Furthermore, subretinal injection of glucose alone reactivates cone OS synthesis.

8:24 AM

The Role of Wide-Field Fluorescein Angiography in the Imaging of Patients in the Inherited Retinal Diseases Clinic

- Cynthia X. Qian, MD
- Kanishka T. Jayasundera, MD,FRANZCO
- Maria Fernanda Abalem, MD, MsC
- Naheed Khan
- Kari Branham, MS
- Dana Schlegel, MS, MPH, CGC

OBJECTIVE To determine the clinical and imaging characteristics that lead towards the use of fluorescein angiography in patients presenting to inherited retinal diseases clinic.

PURPOSE To determine the patient characteristics that lead towards the use of wide-field fluorescein angiography in the inherited retinal diseases (IRD) clinic and the final diagnosis obtained in these patients based on imaging findings and additional workup and testing.

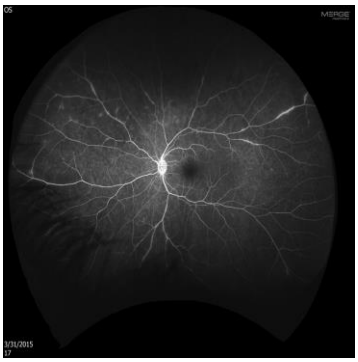
METHODS In this prospective consecutive case series, nine new patients from a total of 450 patients presenting to the IRD clinic practice of a single retinal dystrophy specialist (JT) over a 6 month period were included. These parents were referred to the IRD clinic for presumed retinal degeneration and all necessitated wide-field Optos fluorescein angiography following initial clinical examination, color photography and optical coherence tomography. The clinical and imaging characteristics of these patients prompting fluorescein angiography and further clinical testing including uveitic workup, genetic testing and anti-retinal antibodies panels were reviewed.

RESULTS Seventeen eyes of nine patients showed signs of retinal vasculitis and vascular leakage. Only 1/9 patient presented with unilateral retinal findings. The reasons for

initiating fluorescein angiography studies included: signs of intraocular inflammation and vitreous cells (5/9, 56%), strong personal and familial history of autoimmune conditions (4/9, 44%), and marked asymmetry of presentation between the two eyes (1/9, 11%). The final diagnosis of these patients upon further testing include: posterior uveitides, (5/9, including panuveitis, TB chorioretinitis, and birdshot chorioretinitis), autoimmune retinopathy (2/9), AZOOR (1/9), and cone-rod degeneration (1/9).

CONCLUSION Patients who present to IRD clinic with signs of intraocular inflammation may have a uveitic or an autoimmune masquerading condition. A fluorescein angiography study and additional studies are recommended when clinical signs are atypical, asymmetrical, inflammatory, or suggest strong autoimmune associations.

TAKE HOME MESSAGE Patients who present to IRD clinic with signs of intraocular inflammation may have a uveitic masquerading condition. A fluorescein angiography study and additional studies are recommended.



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