AB037. rAAV mediated PEX1 gene augmentation improves visual function in a mouse model for Zellweger spectrum disorder

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Background: Zellweger spectrum disorder (ZSD) is an autosomal recessive disease caused by mutations in any one of 13 PEX genes whose protein products are required for peroxisome assembly. Retinopathy leading to blindness is one of the major handicaps faced by affected individuals, but treatment for this is supportive only. To test whether we could improve visual function in ZSD, we performed a proof-of-concept trial for PEX1 gene augmentation therapy using the Pex1-G844D mouse model, which bears the equivalent to a common human mutation. This model exhibits a gradual decline in scotopic ffERG response, an always residual photopic ffERG response, diminished visual acuity, and cone and bipolar cell anomalies.
Methods: We administered subretinal injections of a PEX1-containing viral vector (AAV8.CMV.hPEX1.HA) to 2 mouse cohorts of 5 or 9 weeks of age. A GFP-containing vector was used as a control in the contralateral eye of each animal. Efficient expression of the virus was confirmed by retinal histology/immunohistochemistry, and its ability to recover peroxisome import was confirmed *in vitro*. Preliminary ffERG and optokinetic (OKN) analyses were performed on a subset of animals at 8, 16, and 20 weeks after gene delivery. Final ffERG and OKN measures were performed when each cohort reached 32 weeks of age (23 or 27 weeks post injection).
Results: Preliminary ffERG and OKN analyses at 8 weeks post injection showed mildly better retinal response and visual acuity, respectively, in the PEX1-injected eyes, as did ffERG analysis when each cohort reached 25 weeks of age (16 or 20 weeks after gene delivery). This effect was more pronounced in the cohort treated at 5 weeks of age, when ffERG response is highest in Pex1-G844D mice. At 32 weeks of age, the ffERG response in the PEX1-injected eyes was double that of GFP-injected eyes, on average, though there was no change in OKN. Furthermore, in PEX1-injected eyes the photopic ffERG response improved over time, and the decline in scotopic b-wave amplitude was ameliorated compared to un-injected eyes.
Conclusions: AAV8.CMV.hPEX1.HA was subretinally delivered into the left eye of 5- and 9-week-old Pex1-G844D retina. Successful expression of the protein with no gross histologic side effect was observed. Neither the injection, nor exposure to the AAV8 capsid or the transgenic protein negatively altered the ERG or OKN response. At 5–6 months after gene delivery, therapeutic vector-treated eyes showed improved ERG compared to control eyes, on average, in both the "prevention" and "recovery" cohorts. This implies clinical potential of gene delivery to improve vision in patients with ZSD. Retinal immunohistochemistry (to visualize retinal cell types) and biochemical analyses will be performed on treated and untreated retinas, and may inform the mechanism of ERG improvement.
Keywords: Retinal gene therapy; peroxisome disorder; Zellweger spectrum disorder (ZSD); PEX1

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