Efficacy of Gene Therapy in Restoring Vision in Leber's Congenital Amaurosis.

Elizabeth O'Donnell BSc. (Hons.) Natural Sciences, BSc. Pharmaceutical Sciences.
Faculty of Science, Open University, Milton Keynes. UK.

Introduction

*Leber's congenital amaurosis (LCA) is a devastating form of retinal degeneration caused by mutations in up to 14 genes.
*The focus of this research is mutation in gene RPE65. RPE65 deficiency disrupts the visual cycle and progressively causes photoreceptor loss.
*Evidence from pre-clinical animal studies and human clinical trials has shown that gene RPE65 replacement by sub-retinal injection is both safe and effective.
Objectives of this research
*Detailed analysis of the efficacy of gene therapy in restoring vision.
*Evaluation of the limitations of gene therapy in patients with LCA.
*Future directions for the development of gene therapy for restoring vision in LCA.

Methods & Materials

The literature search involved searching databases including "Web of Science," "Science Direct," "Academic SearchComplete,""BioMedCentral," "Springerlink Journals," using keywords "Leber's congenital amaurosis" "Gene therapy" "RPE65" "Vector" in different combinations and restricting dates to 1985 – 2014. Prompt criteria was used to critically evaluate, mostly primary journal articles reporting animal study results and/or human clinical trial data. Secondary sources included clinicaltrials.gov

Results

Efficacy of gene therapy for Leber's Congenital amaurosis.
In clinical trial's patients received RPE65 gene replacement by subretinal vector injection into the eye with worst visual acuity – figure 1.

1) Bainbridge et al., (2008). Three young adults received gene therapy. Patient 3 demonstrated 100 times improvement in sensitivity compared to baseline and profound improvement navigating an obstacle course.

2) Maguire et al., (2009). A pupillometer recorded pupil images to measure pupillary light reflexes before and after gene therapy in 12 patients aged 8-44 years. The results indicate that improvements correlated with age but not dose with children benefitting the most, see figure 2.

3) Jacobson et al., (2012) observed that a patient in the first decade of life had retinal degeneration as severe as a patient in their 30's and no simple correlation existed between photoreceptor loss and age .

Uncertainties and limitations of gene therapy for Leber's Congenital Amaurosis.
Cideciyan et al., (2012). Optical coherence tomography showed progressive photoreceptor loss despite significant visual improvements in 15 participants aged 7-29 years - figure 3.

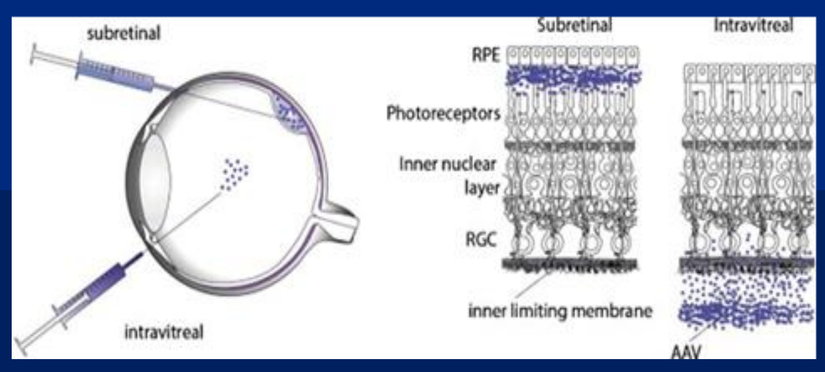

Figure 1. (Left) Diagram of subretinal and an intravitreal injection of vector into a primate eye. (Right) Subretinal injection is targeted at RPE cells at the back of the retina while intravitreal injection into the vitreous of the eye targets ganglion cells. Credit_Image (Dalkaraa and Sahela., 2014).

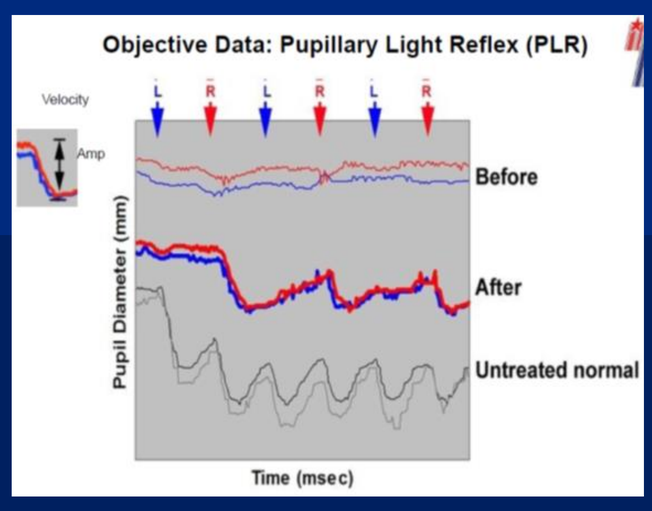

Figure 2. Pupillary light reflex improves in the eye receiving gene therapy with constriction of pupil diameter size (mm) after a light stimulus midway between baseline and a normal untreated eye. (Image_credit Maguire et al., 2009)

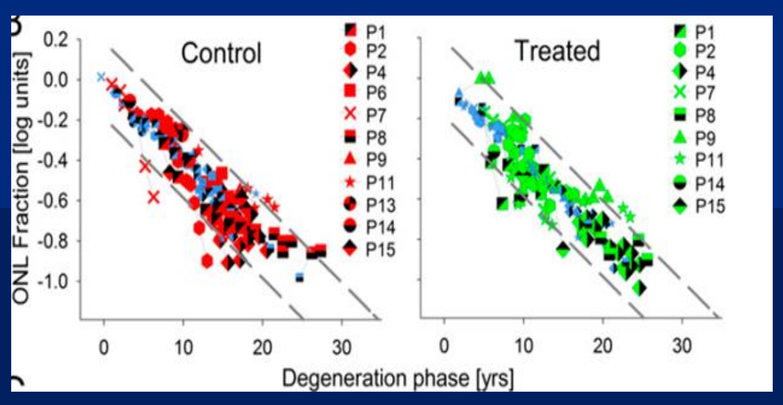

Figure 3. ONL thickness in untreated retinal areas (Left) and treated retinal areas (Right.) No significant differences were observed in retinal degeneration in untreated compared to treated eyes. (Image_credit Cideciyan et al.,2012)

Future directions.

1) Combinational gene therapy strategies including administration of neurotrophic and anti-apoptotic factors to maintain photoreceptor survival long term. (Cideciyan et al.,2012)
2) Dalkara et al., (2014) have developed a new vector that can be injected into vitreous of eye and delivers genes to the retina. It has the advantage of not requiring surgery.

Conclusion

1) Research to identify which neurotrophic factors maintain photoreceptor survival.
2) Research needed to develop new vector gene delivery systems.
3) This study recommends that selection criteria should be based on pre-imaging studies which assesses retinal degeneration on an individual basis irrespective of age.
5) Large scale studies of patient populations monitoring gene therapy safety and efficacy at higher doses and for longer periods.
6) Remarkable successes of gene therapy in improving vision provides hope to sufferers of this once incurable disease.

Contact
Email: eo793@my.open.ac.uk

References.

1) Bainbridge, J.W.B; Ophth, F.R.C; Smith, A.J; Barker, S.S; Robbie, S; Ophth, M.R.C; Henderson, R; Balaggan, K; Viswanathan, A; Holder, G.E; Stockman,S; Tyler, N; Petersen-Jones, S; Bhattacharya, S.S; Thrasher, A.J; Fitzke, F; Carter, B.C; Rubin, G.S; Moore, A.T; Ali, R.R; (2008) "Effect of Gene Therapy on Visual Function in Leber's Congenital Amaurosis" N Engl J Med, vol. 358, pp. 2231-9.
2) Cideciyan, A.V; Jacobson S.G; Beltranb, W.A; Sumarokaa, A; Swidera, M; Iwabeb, S; Romana, A.J; Olivaresa, M.B; Schwartza, S.S; Komáromyb, A.M; Hauswirthd, W.W; Aguirre, G.D; (2012) "Human retinal gene therapy for Leber's congenital amaurosis shows advancing retinal degeneration despite enduring visual improvement." Available [Online] www.pnas.org/cgi/doi/10.1073/pnas.1218933110 (accessed 04/04/2014)
3) Dalkara, D; Sahel, J.(2014) "Gene therapy for inherited retinal degenerations" Available [Online] http://www.sciencedirect.com.libezproxy.open.ac.uk/science/article/pii/S1631069114000031 (Accessed 05/06/2014)
4) Jacobson, S.G, Cideciyan, A.V, Ratnakaram,R; Heon, E; Schwartz,S.B, Roman, A.J, Peden,M.C, Aleman T,S; Boye, S.L, Sumaroka,A, Conlon, T.J, Calcedo,R, Pang ,J.J, Erger,K.E, Olivares,M.B, Mullins,C.L, Swider,M, Kaushal, S, Feuer,W.J, Iannaccone ,A, Fishman ,G.A, Stone, E.M, Byrne, B.J, Hauswirth, W.W. (2012) "Gene therapy for leber congenital amaurosis caused by RPE65 mutations: Safety and efficacy in 15 children and adults followed up to 3 years." Arch Ophthalmol 130(1):9–24
5) Maguire, A.M; High, K.A; Auricchio, A; Wright, J.F; Pierce, E.A; Testa, F; Mingozzi, F; Bennicelli, J.L; Ying, G; Rossi, S; Fulton, A; Marshall, K. A. (2009) "Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial" Lancet, vol. 374, pp. 1597–605.