OCULAR GENE THERAPY GROUP: A MULTI-DISCIPLINARY APPROACH TO GENE THERAPY TREATMENT FOR PATIENTS WITH RPE65-MEDIATED RETINAL DYSTROPHY

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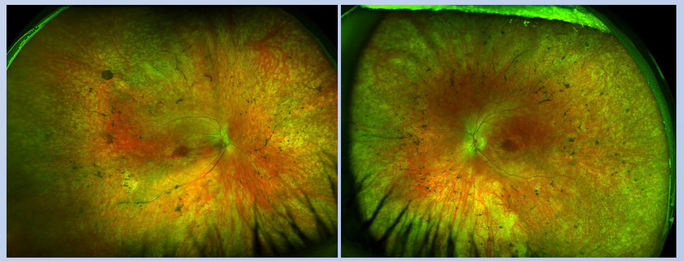
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INTRODUCTION

Inherited retinal diseases (IRD)are the second commonest cause of severe visual impairment in childhood and the most frequent in the working age population [1]. There are several hundred known responsible genes that cause a heterogeneous group of conditions.

In the *RPE65* gene, over 60 different mutations have been identified that are associated with a heterogeneous group of inherited retinal dystrophies including Leber's congenital amaurosis (LCA) and autosomal recessive retinitis pigmentosa (RP)[2]. These conditions usually present with progressive loss of vision from birth or early childhood and nystagmus. Mutations in the *RPE65* gene account for approximately 2% of cases of recessive RP and approximately 16% of cases of LCA in humans[3].

In 2019, NICE approved Voretigene Neparvovec (Luxturna) as a licenced treatment for RPE65-mediated IRD. This prompted the formation of the Manchester Ocular gene therapy group.



Optos wide-field digital imaging of a patient with RPE65

METHODS

The identification of suitable patients is the key first stage of instigation of gene therapy treatment. To ensure that the correct patients are selected and treated, we adopted a multidisciplinary team (MDT) approach. The MDT comprises of clinical geneticists, paediatric ophthalmologists, genetic counsellors, clinical scientists and vitreoretinal surgeons. MDT meetings are convened bimonthly to discuss genetics (whether the genetic RPE65 variant identified in the patient meets the criteria for pathogenicity), ophthalmic investigations and assess eligibility for treatment for the patients who have been referred. At the same time, patient knowledge, expectations and consent are discussed, and a pre-treatment / post-treatment follow up plan is put in place.

Patients were identified from the genetic database, their molecular diagnoses re-evaluated and then discussed by the MDT. Eligible individuals are invited for assessment, including imaging, visual fields, electrodiagnostic evaluation and consultations with the genetic counsellor, vitreoretinal surgeon and paediatric ophthalmologist (depending on patient age).

Once a patient with RPE65 IRD has been discussed in the MDT and confirmed to be suitable for treatment from a genetic perspective, they then need to fulfil three clinical criteria before the treatment can go ahead. The patient needs to have-

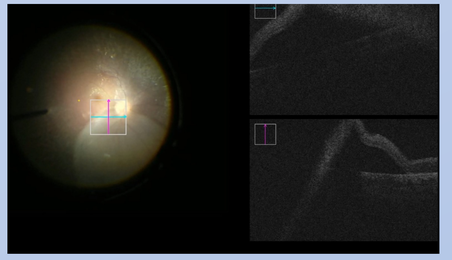
1) three or more-disc areas without atrophy or pigmentary degeneration within the posterior pole;

2) OCT showing more than a 100-micrometre thickness in an area of the retina within the posterior pole;

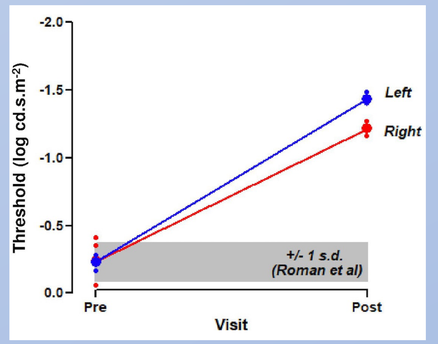
3) a remaining visual field (VF) within 30^{o} of fixation.

Pre and post-treatment imaging, electrophysiology and psychophysics are therefore crucial to assess patient eligibility for treatment, and also assess the impact of treatment on visual function, particularly when any treatment benefit is unlikely to be measured by visual acuity alone. Ganzfeld and Multifocal electroretinograms are conducted using ISCEV standards, and Visual fields are conducted using static 10-2 macular threshold perimetry. Contrast sensitivity and colour vision are tested. Low luminance visual acuity is tested using three levels of illumination down to 0.34cd.m^{-2}, and dark-adapted retinal sensitivity is tested using FST. Imaging and OCT is carried out at each post-operative visit, and psychometric testing pre-operatively, at 3-6 months post-operatively and after one year.

RESULTS



Intraoperative OCT confirming subretinal injection



Patient one: Full-field scotopic threshold - pre and post treatment of both eyes

- *Excellent repeatability R and L, with variability within normal limits (see data from Roman et al).*
- *Both eyes show marked improvement in scotopic sensitivity, by a factor of 10 (1 log unit) in the right eye and by a factor of 16 (1.2 log units) in the left eye.*

From Jan 2020 till May 2021, six patients (age 7-38 years) met all criteria and five opted for surgery. One patient declined surgery as he was unsure about the efficacy, longevity and potential risks of the treatment and surgery. Two patients have received bilateral subretinal injection of Voretigene Neparvovec. Three patients have had only one eye treated and are awaiting the second eye to be done in due course. All patients have had subjective improvement in peripheral and low luminance vision as well as improvement of rod function as elicited by increased retinal sensitivity on psychophysical testing. One patient reported loss of central vision, despite improvement of his peripheral and low luminance vision on psychophysical testing.

CONCLUSION

Gene replacement approaches for RPE65-mediated IRD in the clinical setting are associated with excellent preliminary outcomes and positive patient experiences. We have developed a consistent and precise approach to clinical / molecular pre-treatment assessment. Consent discussions, in particular, necessitated input of different health professionals. Overall, the MDT-based approach optimises surgical outcomes and provides comprehensive support for patients and families.

References:

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