SENSORY SYSTEMS

Promising results in a gene therapy trial for retinal disease

Choroideremia is a degenerative disease of the retina caused by mutations in the *CHM* gene, which encodes Rab escort protein 1 (REP1), ultimately leading to retinal cell degeneration and blindness. In a recent phase I, multicentre clinical trial, Robert MacLaren from Oxford Eye Hospital, UK and his colleagues have demonstrated that gene therapy with an adeno-associated viral 2 (AAV2) vector containing the *CHM* gene improves visual acuity and retinal sensitivity in patients with choroideremia.

In the majority of patients, choroideremia is associated with functionally null mutations, which result in complete loss of the retina, choroid and retinal epithelial pigment. However, good visual acuity is maintained until degenerative changes and thinning of the retinal pigment epithelium become apparent in the fovea, usually in the fifth decade of life. The small size of the protein coding sequence, and the fact that AAV2 is known to be safe for use in humans and has distinct tropism for retinal pigment epithelial cells, made AAV2 gene therapy an attractive treatment option for the researchers.

The study was carried out in six male patients aged 35–63 years at different stages of retinal degeneration. Owing to the rate of degeneration, the area of tissue remaining that is available for transduction with the vector varies according to disease progression. The researchers injected the AAV2 vector into the subretinal space of one eye in each patient. At baseline and 6 months after treatment, best corrected visual acuity was measured using the standard Early Treatment for Diabetic Retinopathy Study protocol, and microperimetry was used to map retinal sensitivity.

Two patients who started the study with advanced choroideremia had improved visual acuity at 6 months, with one gaining over two lines and the other gaining over four lines on the Snellen test. The other four patients, who had near-normal vision at baseline, also had improved visual acuity. None of the participants had any detrimental effects from subretinal injection of the vector, which causes retinal detachment, and in all patients the increase in retinal sensitivity in the treated eye correlated with the vector dose administered per mm² of surviving retina. By contrast, in the untreated control eyes, microperimetry measurements indicated a decline in visual function over the course of the study.

In a previous trial of gene therapy, in patients with Leber congenital amaurosis, concerns were raised that retinal degeneration might continue despite successful transduction and prevention of visual loss. In the study by MacLaren *et al.*, however, retinal cell layers were fairly well-preserved, and there was no evidence of thinning of the retina on completion of the study. These results suggest that gene therapy with AAV2 might be an effective treatment option to prevent sight loss in patients with choroideremia before the onset of retinal thinning. Furthermore, this study highlights the potential of a gene therapy approach in other sight-threatening diseases.

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Original article MacLaren, R. E. *et al.* Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial. *Lancet* doi:10.1016/S0140-6736(13)62117-0

Further reading Cideciyan, A. V. *et al.* Human retinal gene therapy for Leber congenital amaurosis shows advancing retinal degeneration despite enduring visual improvement. *Proc. Natl Acad. Sci. USA* **110**, E517–E525 (2013)