Gene therapy shows long-term benefit for treating rare blindness

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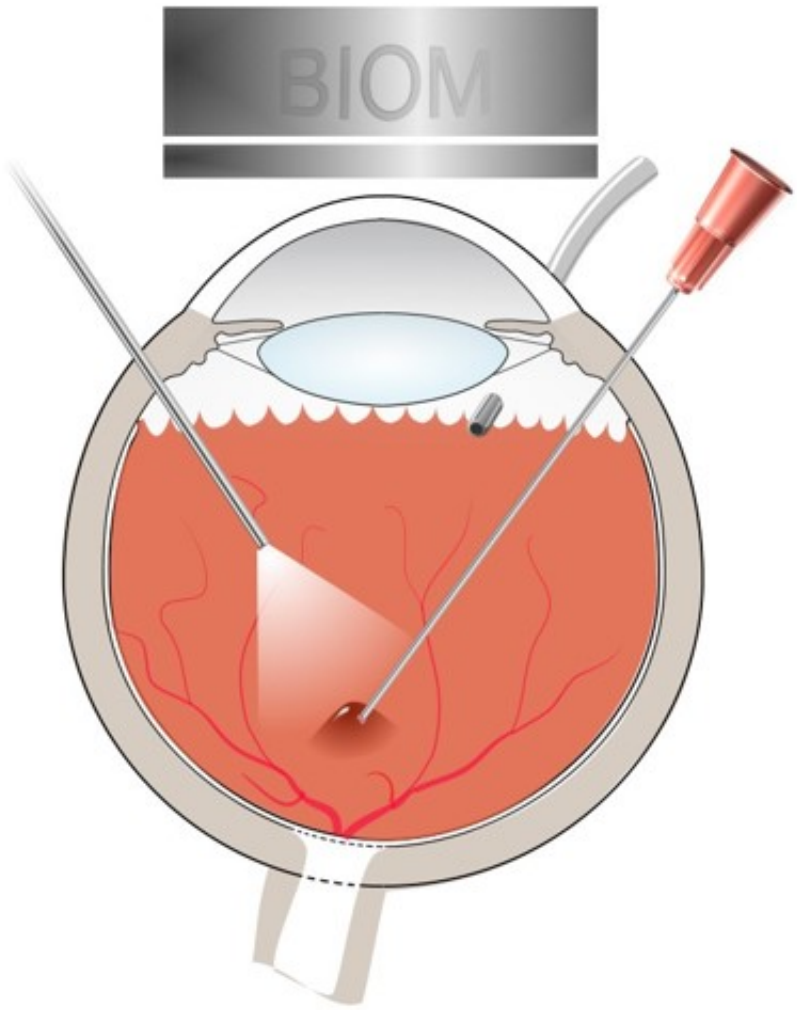

Operations have been taking place at the John Radcliffe Hospital, Oxford to inject a virus into the eye to deliver billions of healthy genes as part of University of Oxford research to replace a key missing gene for choroideremia sufferers. A diagram illustrating how the eye is operated on to deliver the gene

therapy under the retina. Step 2 - injection of the virus under the retina. Credit: University of Oxford

Pioneering gene therapy has restored some vision to patients with a rare form of genetic blindness for as long as four years, raising hopes it could be used to cure common causes of vision loss, new University of Oxford research published today shows.

A technique which involves injecting a virus into the eye to deliver billions of healthy genes to replace a key missing gene for choroideremia sufferers has provided sustained improvement in vision for up four years for some patients.

This provides the strongest evidence so far in humans that the effects of gene therapy are potentially permanent and could therefore provide a single treatment cure for many types of inherited blindness. These include retinitis pigmentosa, which affects young people, and age-related macular degeneration, which affects the older age group.

Reporting the results this week in the *New England Journal of Medicine*, doctors from the University of Oxford examined the vision of six patients up to four years after receiving gene therapy at Oxford's John Radcliffe Hospital. These six were the first in the world to have the procedure for choroideremia in a trial funded by the Department of Health and the Wellcome Trust.

The gene therapy treatment was designed to slow or stop sight loss, however, two of the patients experienced a significant improvement in vision that was sustained for at least four years, despite a decline in their untreated eyes over this period. A further three maintained their vision in their treated eyes throughout this period. The sixth patient who had a

lower dose had a slow decline in vision in both eyes.

It is hoped that gene therapy would ideally be applied to patients early in the disease process to prevent sight loss because the treatment is expected to be long lasting. Patients with choroideremia are missing a key gene in their retina and the technique involves injecting a virus to deliver billions of healthy genes to replace the missing gene.

Professor Robert MacLaren, the lead investigator of the study, said: "There have recently been questions about the long term efficacy of gene therapy, but now we have unequivocal proof that the effects following a single injection of viral vector are sustained. Even sharpening up the little bit of central vision that these patients have can give them considerable independence.

"Gene therapy is a new technique in medicine that has great potential. As we learn more about genetics we realise that correcting faulty genes even before a disease starts may be the most effective treatment. Gene therapy uses the infectious properties of a virus to insert DNA into a cell, but the virial DNA is removed and replaced with DNA that is reprogrammed in the lab to correct whichever gene is faulty in the patient.

"In this case, success in getting a treatment effect that lasts at least several years was achieved because the viral DNA had an optimal design and the viral vector was delivered into the correct place, using advanced surgical techniques. In brief, this is the breakthrough we have all been waiting for."

Dr Stephen Caddick, Director of Innovation at the Wellcome Trust, added: "To permanently restore sight to people with inherited blindness would be a remarkable medical achievement.

"This is the first time we've seen what appears to be a permanent change in vision after just one round of treatment. It's a real step forwards towards an era where gene therapy is part of routine care for these patients."

Jonathan Wyatt, the first patient in the world to be treated with this gene therapy is still sight impaired, but he was able to double the level of vision in his treated left eye, which has been maintained for four years so far.

The retired barrister, 68, of Bristol, suffered vision problems since the age of 20. The right eye has continued to degenerate and the left eye is now dominant.

Mr Wyatt, married to Diana, for nearly 30 years, could read 23 letters in eye chart tests prior to the operation but by three-and-a-half years could read 44.

Mr Wyatt said: "I feel very lucky, privileged and honoured to be part of the fantastic John Radcliffe research group. I feel that even though I am the meat in a sandwich, my life will be making a contribution to help others."

"The left eye is much improved to such an extent that I use it mostly to get about these days. It has substantially improved, it is fantastic.

"It has made me more independent, I think I would be more dependent. I think I would feel more cautious about train journeys on my own. Without it I think I would be tapping with a white stick, I think I would have remained cheerful but I would be at home more."

Joe Pepper, a 24-year-old teacher from Croydon, who was the last patient to receive the gene therapy treatment (not in the original cohort

of six), said: "I sat down and began the reading chart test on my treated right eye and I read the first two lines and for the first time in my memory I read on and on.

"I will remember that day for the rest of my life. I could see more than before the operation. I could read four lines beyond where I was earlier. I laughed and shed a tear. It was special.

"Six months on from the surgery the results have been more than I ever imagined. My vision now has a new found clarity and I am no longer putting stress on my vision when reading or looking into the distance. Instead of looking into the distance and seeing outlines of people or trees I am seeing their defined features. At night I now have a new found confidence in dimly lit areas that means I can feel independent and safe after dark.

"Without Professor MacLaren and his team, and their pioneering work I could have lost my sight and for the last 14 years I have feared I could. The work they do is special and I have nothing but thanks to them."

More information: Thomas L. Edwards et al, Visual Acuity after Retinal Gene Therapy for Choroideremia, *New England Journal of Medicine* (2016). DOI: 10.1056/NEJMc1509501

Provided by University of Oxford